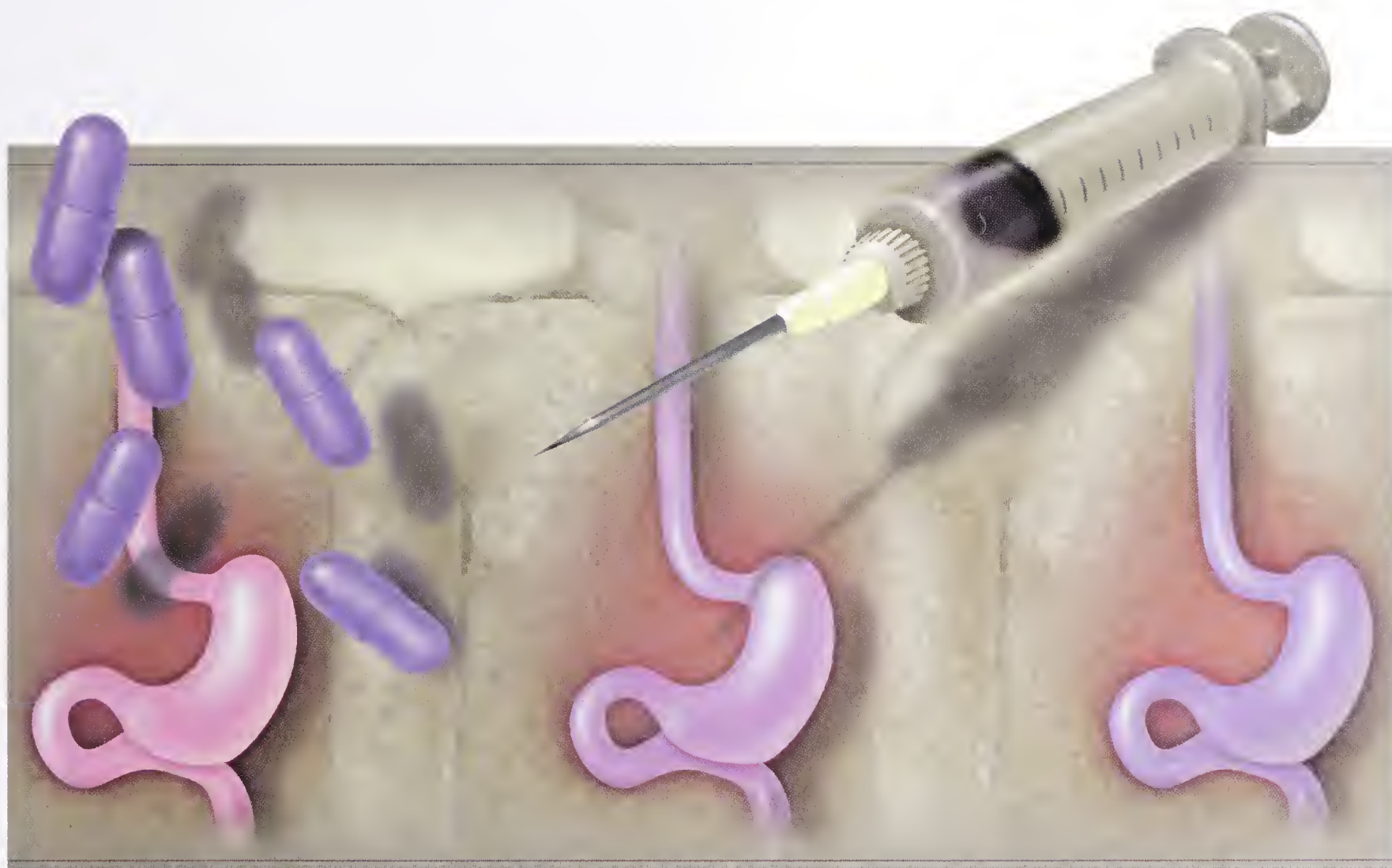


UTMJ

University of Toronto Medical Journal

Volume 78, Number 2/March, 2001

A student-run scientific publication. Established in 1923.



- 88 **Preface**
- 92 **Intravenous Proton Pump Inhibitors and H₂-Receptor Antagonists for the Immediate Treatment of Acute Upper Gastrointestinal Hemorrhage: A Meta-Analysis of Randomized Controlled Trials**
Akash Ghai, George Tomlinson, James Bowen, Christine Papoushek and Allan S. Detsky
- 102 **Oral Contraceptive-Induced Thrombogenesis: A Review**
Andrea K. Boggild, and Yael Friedman
- 108 **Robot-Assisted Surgery: A Review**
Anand Govindarajan
- 114 **Review of Methods Used to Estimate Patient Benefit from Middle Ear Surgery to Correct Unilateral and Asymmetric Conductive Hearing Loss**
Jon Kian Nia, Manohar Bance, and Sharif Missiha

- 117 **Crossword**
- 120 **News and Views**
- 146 **Clinicopathological Correlation**
- 150 **Quick Diagnosis**
- 159 **Morning Report**
- 162 **Technology Review**
- 165 **Medical Research**
- 167 **Book Reviews**

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Table of Contents

- | | |
|---|--|
| <p>88 Preface</p> <p>Gastroenterology</p> <p>92 Intravenous Proton Pump Inhibitors and H₂-Receptor Antagonists for the Immediate Treatment of Acute Upper Gastrointestinal Hemorrhage: A Meta-Analysis of Randomized Controlled Trials
<i>Akash Ghai, George Tomlinson, James Bowen, Christine Papoushek and Allan S. Detsky</i></p> <p>Cardiovascular</p> <p>102 Oral Contraceptive-Induced Thrombogenesis: A Review
<i>Andrea K. Boggild, and Yael Friedman</i></p> <p>Surgery</p> <p>108 Robot-Assisted Surgery: A Review
<i>Anand Govindarajan</i></p> <p>Otolaryngology</p> <p>114 Review of Methods Used to Estimate Patient Benefit from Middle Ear Surgery to Correct Unilateral and Asymmetric Conductive Hearing Loss
<i>Jon Kian Nia, Manohar Bance, and Sharif Missiha</i></p> <p>117 Crossword
<i>Sarah Shaikh and Giovanna Sirianni</i></p> <p>News and Views</p> <p>120 In the Literature
<i>Philippe L. Bedard</i></p> <p>122 Prolific Scientist Profiles:
An Interview with Dr. Charles Tator
<i>Christopher J. Hall</i></p> <p>124 Back to Basics V: An Approach to the Patient with a Life-Threatening Acid-Base Disturbance: The Acidemias
<i>Manish Shah, Murray Beuerlein and Karoon Danayan</i></p> <p>129 Law and Ethics in Medicine:
The Complaints and Discipline Processes for Physicians: What You Need to Know
<i>Aditya Bharatha and Philip Buckler</i></p> <p>133 Evidence-Based Medicine:
The Value of Mammography in Screening for Breast Cancer
<i>Ann M. Stewart</i></p> | <p>135 Forum:
Access to Medicines – The Global Debate Over "Free Trade"
<i>Tanya L. Zakrison and Paul A. Hamel</i></p> <p>141 Use of the Internet by Canadian Physicians and the Influence of the Internet on the Doctor-Patient Relationship
<i>Steve K. Singh</i></p> <p>Clinicopathological Correlation</p> <p>146 A Rare But Deadly Disease
<i>Yael Friedman, Andrea K. Boggild and Liesly Lee</i></p> <p>Quick Diagnosis</p> <p>150 Piero Tartaro, Steven W.H. Hwang and Shoba Subramanian</p> <p>Morning Report</p> <p>159 A Case for Osler
<i>Catherine Chung, Martin C. Chang and Damon Scales</i></p> <p>Technology Review</p> <p>162 Interstitial Laser Photocoagulation: A Clinical Alternative
<i>Lee Chin and Vanessa Choy</i></p> <p>Medical Research</p> <p>165 Canadian Institutes of Health Research: A Genotype for Success
An Interview with Dr. Alan Bernstein
<i>Jewel Samadder</i></p> <p>Book Reviews</p> <p>167 Honest Truths About the Double Helix
<i>Brenda Roy</i></p> <p>168 Evolutionary Psychology for Dummies
<i>Jennifer Gold</i></p> <p>169 For the Voyeur Within Us
<i>Hemant Shah</i></p> <p>170 And How Does that Make You Feel?
<i>Stephanie R. Wiesenthal</i></p> <p>171 Neurological Bible Gets an Update
<i>Paul S. Giacomini</i></p> <p>172 A New Edition of a Medicine Standard
<i>Richard Bitar</i></p> |
|---|--|



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The Editors apologise for any omissions to the above list; this list represents our final version at press time. We will update the list in future issues.

Preface from the Editors

In this second issue of the 78th volume of the *UTMJ*, we again aspire to represent the multifaceted nature of medicine. We aim to interest all patrons, regardless of specialty or stage of training, by providing a collection of highly varied articles. With the second issue, we strive to promote an evidence-based approach by reviewing and re-evaluating topics at the heart of clinical medical practice.

We begin this issue with a fascinating article by Ghai *et al.* that re-examines the necessity of using intravenous proton pump inhibitors and H₂-receptor antagonists in the treatment of acute upper gastrointestinal hemorrhage. Through a meta-analysis, the authors consider the evidence underlying this common medical practice, and question the true efficacy of this treatment. Our second feature article continues the evidence-based theme by examining the association between oral contraceptives and thrombogenesis. In this detailed piece, Boggild and Friedman delve into this complex issue in a highly comprehensive manner. It is likely to be an invaluable learning tool for any clinician prescribing oral contraceptives. In our third piece, Govindarajan reviews recent developments in the emerging field of robot-assisted surgery. The article critically examines possible risks and benefits of this new technology, and provides a balanced view of the medical and economical factors involved. Finally, Nia *et al.* examine the techniques currently used to evaluate the success of middle ear surgery for conductive hearing loss. The authors present preliminary data that support the validity of using these methods.

In the News and Views section, the theme of evidence-based medicine is continued by an evaluation of mammography as a screening tool for breast cancer, a timely discussion of a highly contentious issue. We also maintain our tradition of including a forum that aims to present information surrounding a controversial topic in a medically-related field. This issue features a debate on the access to essential medicines in the third world. Zakrisson and Hamel explore this topic from the viewpoint of the pharmaceutical company, Médecins sans Frontières, and through a human rights perspective. We con-

tinue our popular Back to Basics section with a comprehensive review of assessing patients presenting with potentially fatal acidemias. The News and Views section also profiles the changes occurring at the Canadian Institutes of Health Research through an interview with its president, Dr. Alan Bernstein. The CIHR provides a view into the research evolution occurring in Canada today. In our prolific scientist profile, we present an interview with Dr. Charles Tator, an internationally renowned neurosurgeon who has won numerous accolades for both his research and clinical skills.

In the Technology Review section, a developing cancer therapy called interstitial laser photocoagulation is presented. A broad approach is used to describe this new innovation in oncological treatments, as well as the obstacles preventing its widespread use in therapy. We have also continued our new tradition of including a challenging crossword for your enjoyment.

We would like to take this opportunity to encourage all patrons to visit our revamped website at <http://www.utmj.org>.

Prateek Lala
Valerie Panet-Raymond
Editors-in-Chief

We regret the omission of acknowledgment for Karen Petrucci's work on Figures 1, 2 and 3 in the last issue of the UTMJ Back-to-Basics feature, entitled "Fracture Management" (*UTMJ*, 78(1):45, 2000).



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LIPITOR is a cholesterol-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, the first step in the biosynthesis of cholesterol.

LIPITOR lowers total cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver. It also increases the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell surface for LDL uptake and metabolism of Low Density Lipoprotein (LDL).

LIPITOR reduces total cholesterol (LDL-C) and the number of LDL particles. LIPITOR also reduces Very Low Density Lipoprotein (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of lipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Increased triglyceride level due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Elevated triglyceride is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Atorvastatin is rapidly absorbed after oral administration, maximum plasma concentrations occur within 1 to 2 hours. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions.

Mean distribution of atorvastatin is approximately 381 litres. Atorvastatin is ≥98% bound to plasma proteins. Atorvastatin is extensively metabolized by cytochrome P-450 3A4 to ortho- and para-hydroxylated derivatives and to various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites.

INDICATIONS AND CLINICAL USE

LIPITOR (atorvastatin calcium) is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated total cholesterol, (total C), LDL-C, TG and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

- Primary hypercholesterolemia (Type IIa);
- Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern;
- Dysbetalipoproteinemia (Type III);
- Hypertriglyceridemia (Type IV);
- Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly to moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%) and increased high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25 - 56%) and LDL-C levels (23 - 40%). Chylomicrons, which characterize Types I and V, have not been measured in clinical studies in patients with high TG levels (>11 mmol/L).

In an open-label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and LDL-C + VLDL-C levels (34-58%).

In an open-label study in patients with homozygous familial hypercholesterolemia (FH) LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients (see PHARMACOLOGY, Clinical Studies).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACOLOGY, Clinical Studies.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism) and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG < 4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

$$\text{LDL-C (mmol/L)} = \text{total-C} - \{ [0.37 \times (\text{TG} + \text{HDL-C})] \}$$

$$\text{LDL-C (mg/dL)} = \text{total-C} - \{ [0.2 \times (\text{TG} + \text{HDL-C})] \}$$

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

The Atorvastatin Versus Revascularization Treatments (AVERT) study examined the effect of intensive lipid-lowering in patients with stable coronary artery disease and LDL-C at least 3.0 mmol/L in patients referred for percutaneous transluminal coronary angioplasty (PTCA). Patients were randomised for 18 months to LIPITOR 80 mg daily or to PTCA with usual medical care which could include lipid metabolism regulators. The results of the AVERT study should be considered as exploratory since several limitations may affect its design and conduct. In the medical-treated group with LIPITOR there was a trend for a reduced incidence of ischemic events and time to first ischemic event. The results also suggest that intensive treatment to target LDL-C levels with LIPITOR is **additive and complementary** to angioplasty and would benefit patients referred for this procedure (see SELECTED BIBLIOGRAPHY).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions

Since LIPITOR is an HMG-CoA reductase inhibitor has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. LIPITOR is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme (see WARNINGS, Muscle effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450-mediated interactions).

Hepatic Effects

Elevations in serum transaminases greater than three times the upper limit of normal occurred in 11 patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted, the elevated serum transaminase levels returned to pretreatment levels. The increases were generally not associated with any other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated frequently, and then performed more frequently.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR; if such a condition should develop during therapy, the drug should be discontinued.

Muscle Effects

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibrin acid derivatives, erythromycin, clarithromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of pharmacokinetic studies conducted in healthy subjects with erythromycin and clarithromycin, the benefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions). Rhabdomyolysis has been reported in very rare cases with LIPITOR (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been reported with HMG-CoA reductase inhibitors. LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

The effects of atorvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol on cardiovascular morbidity or mortality or total mortality have not been established.

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

Effect on the Lens

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Effect on Ubiquinone (CoQ₁₀) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY).

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) levels. Until further experience is obtained, it is suggested, where feasible, that measurements of serum Lp(a) be followed up in patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY).

Hypersensitivity

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

Use in Pregnancy

LIPITOR is contraindicated during pregnancy (see CONTRAINDICATIONS).

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause harm to the fetus when administered to pregnant women.

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

Nursing Mothers

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Geriatric Use

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see PHARMACOLOGY, Human Pharmacokinetics; SELECTED BIBLIOGRAPHY).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency (creatinine clearance <30 mL/min (<0.5 mL/sec)); the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects; PRECAUTIONS, Drug Interactions).

Refer also to DOSAGE AND ADMINISTRATION.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Pharmacokinetic Interaction Studies and Potential Drug Interactions

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see also Geriatric Use; Renal Insufficiency; Patients with Severe Hypercholesterolemia).

Concomitant Therapy with Dther Lipid Metabolism Regulators: Combined drug therapy should be approached with caution as information from controlled studies is limited.

Bile Acid Sequestrants:

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to that with LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone. However, the combination drug therapy was less effective in lowering the triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least two hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid): Although there is no experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration (see WARNINGS, Muscle Effects).

Coumarin Anticoagulants: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTED BIBLIOGRAPHY).

Digoxin: In healthy subjects, digoxin pharmacokinetics at steady-state were not significantly altered by coadministration of digoxin 0.25 mg and LIPITOR 10 mg daily. However, digoxin steady-state concentrations increased approximately 20% following coadministration of digoxin 0.25 mg and LIPITOR 80 mg daily (see Human Pharmacokinetics). Patients taking digoxin should be monitored appropriately.

Antihypertensive agents (amlodipine): In clinical studies, LIPITOR was used concomitantly with antihypertensive agents without evidence to date of clinically significant adverse interactions. In healthy subjects, atorvastatin pharmacokinetics were not altered by the coadministration of LIPITOR 80 mg and amlodipine 10 mg at steady state (see Human Pharmacokinetics).

Dral Contraceptives and Hormone Replacement Therapy: Coadministration of LIPITOR with an oral contraceptive, containing 1 mg norethindrone and 35µg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive. In clinical studies, LIPITOR was used concomitantly with estrogen replacement therapy without evidence to date of clinically significant adverse interactions.

Antacids: Administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Cimetidine: Administration of cimetidine with LIPITOR did not alter plasma concentrations or LDL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, some macrolide antibiotics (i.e. erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), or the antidepressant, nefazodone, may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY). Caution should thus be exercised with concomitant use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Endocrine Function; DOSAGE AND ADMINISTRATION; SELECTED BIBLIOGRAPHY).

In healthy subjects, coadministration of maximum doses of both atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g. pre-existing prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION).

Antipyrine: Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin): In healthy adults, coadministration of LIPITOR (10 mg QD) and azithromycin (500 mg QD) did not significantly alter the plasma concentrations of atorvastatin. However, coadministration of atorvastatin (10 mg QD) with erythromycin (500 mg QID) or clarithromycin (500 mg BID), which are both CYP 3A4 inhibitors, increased plasma concentrations of atorvastatin approximately 40% and 80%, respectively (see WARNINGS, Muscle Effects; Human Pharmacokinetics).

Patients with Severe Hypercholesterolemia: Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions; DOSAGE AND ADMINISTRATION).**

Drug/Laboratory Test Interactions

LIPITOR may elevate serum transaminase and CPK levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid-lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

TABLE 1. Associated Adverse Events Reported in ≥1% of Patients in Placebo-Controlled Clinical Trials		
	Placebo % (n=270)	LIPITOR % (n=1122)
GASTRDINTESTINAL		
Constipation	1	1
Diarrhea	1	1
Dyspepsia	2	1
Flatulence	2	1
Nausea	0	1
NERVOUS SYSTEM		
Headache	2	1
MISCELLANEOUS		
Pain	<1	1
Myalgia	1	1
Asthenia	<1	1

The following additional adverse events were reported in clinical trials; not all events listed below have been associated with a causal relationship to LIPITOR therapy: Muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia.

Post-marketing experience: Very rare reports: severe myopathy with or without rhabdomyolysis (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Drug Interactions). Isolated reports: thrombocytopenia, arthralgia and allergic reactions including urticaria, angioneurotic edema, anaphylaxis and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis). These may have no causal relationship to atorvastatin.

Ophthalmologic observations: see PRECAUTIONS.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

OOSAGE AND AADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the American Heart Association

(AHA) Step 1 diet] before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented. Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia, Including Familial Combined Hyperlipidemia The recommended dose of LIPITOR is 10 mg once a day. The majority of patients achieve and maintain target cholesterol levels with LIPITOR 10 mg/day. A significant therapeutic response is evident within two weeks, and the maximum response is usually achieved within two to four weeks. The response is maintained during chronic therapy.

Doses can be given at any time of the day, with or without food, and should preferably be given in the evening. Doses should be individualized according to baseline LDL-C and/or TG levels: the desired LDL-C and/or TG target (see the Detection and Management of Hypercholesterolemia, Working Group on Hypercholesterolemia and other Dyslipidemias [Canada] and/or the US National Cholesterol Education Program [NCEP]), the goal of therapy and the patient's response. Adjustments of dosage, if necessary, should be made at intervals of four weeks or more. The recommended dose range for most patients is 10 to 40 mg/day. The maximum dose is 80 mg/day, which may be required in a minority of patients (see section below).

Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

The following reductions in total cholesterol and LDL-C levels have been observed in two dose-response studies, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia.

TABLE 2. Dose-Response in Patients With Mild to Moderate Hypercholesterolemia
(Mean Percent Change from Baseline)*

Lipid Parameter	LIPITOR Dose (mg/day)			
	10 (N=22)	20 (N=20)	40 (N=21)	80 (N=23)
Total-C: 7.1 mmol/L ^b (273 mg/dL) ^b	-29	-33	-37	-45
LDL-C: 4.9 mmol/L ^b (190 mg/dL) ^b	-39	-43	-50	-60

*Results are pooled from 2 dose-response studies.

^bMean baseline values.

Severe Dyslipidemias:

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions).

Concomitant Therapy

See PRECAUTIONS, Drug Interactions.

Dosage in Patients With Renal Insufficiency

See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance

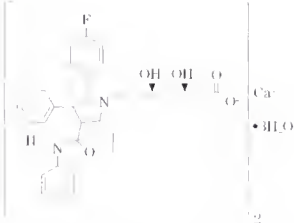
Proper Name: Atorvastatin calcium

Chemical Name: [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2/1) trihydrate

Empirical Formula: (C₃₁H₃₄FN₂O₅)₂Ca•3H₂O

Molecular Weight: 1209.42

Structural Formula:



Description: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Tablet Composition:

Each tablet contains either 10 mg, 20 mg or 40 mg atorvastatin as the active ingredient. Each tablet also contains the following non-medical ingredients: calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, polysorbate 80 and simethicone emulsion.

Stability and Storage Recommendations:

Store at controlled room temperature 15 to 25°C.

AVAILABILITY OF OOSAGE FORMS

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg and 40 mg atorvastatin per tablet.

10 mg: White, elliptical, film-coated tablet, coded "10" on one side and "PD 155" on the other. Available in bottles of 90 tablets.

20 mg: White, elliptical, film-coated tablet, coded "20" on one side and "PD 156" on the other. Available in bottles of 90 tablets.

40 mg: White, elliptical, film-coated tablet, coded "40" on one side and "PD 157" on the other. Available in bottles of 90 tablets.

References:

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For a copy of the Product Monograph or full Prescribing Information, please contact.



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Intravenous Proton Pump Inhibitors and H₂-Receptor Antagonists for the Immediate Treatment of Acute Upper Gastrointestinal Hemorrhage: A Meta-Analysis of Randomized Controlled Trials

Akash Ghai, B.Sc., M.D. (OT0)

George Tomlinson, Ph.D.

James Bowen, B.Sc.Pharm., M.Sc.

Christine Papoushek, Pharm.D.

Allan S. Detsky, M.D., Ph.D.

Abstract

A meta-analysis was conducted to determine the efficacy of intravenous proton pump inhibitors (PPIs) and H₂-receptor antagonists (H₂RAs) for the immediate treatment of acute non-variceal upper gastrointestinal (GI) hemorrhage. Collected randomized controlled trials were divided into two groups based on the method of treatment administration. Studies were labeled “primary” treatment models when initial treatment with intravenous H₂RAs or PPIs was directly compared to initial treatment with intravenous placebo, with both groups usually receiving oral H₂RAs or PPIs thereafter. Studies were labeled “secondary” treatment models when both intravenous and oral H₂RAs or PPIs were compared to various control therapeutic strategies. Among 1,797 patients from 8 trials in the primary group, the odds ratios (OR) for continued bleeding, operation-need and mortality were 0.859 (95% CI, 0.677 to 1.105), 0.817 (95% CI, 0.527 to 1.267) and 1.336 (95% CI, 1.066 to 1.676) respectively. Among 2,841 patients from 17 trials in the secondary group, the ORs for continued bleeding, operation need and mortality were 0.762 (95% CI, 0.603 to 0.964), 0.895 (95% CI, 0.685 to 1.170) and 0.901 (95% CI, 0.627 to 1.294) respectively. Thus, this meta-analysis cannot establish the therapeutic benefit of initial intravenous acid reduction therapies given prior to oral medication for patients with acute nonvariceal upper GI hemorrhage. Clinicians initiating acid reduction therapy may wish to consider the oral route of delivery.

Introduction

Upper gastrointestinal (GI) bleeding is a common clinical problem with an annual incidence of 102 admissions per 100,000.¹ A 10% mortality rate has been associated with these patients after hospital admission.^{2,3} Empiric treatment for most patients presenting to emergency wards consists of volume replacement, naso-gastric suction and acid-reducing agents.

Acid-reduction therapies such as H₂-receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) are commonly used for the

treatment of upper-GI bleeding.⁴ This practice is based on *in vitro* studies conducted in the 1970s which demonstrated that raising intragastric pH reduced clot lysis and increased platelet aggregation.^{5,6} Since most patients are felt to be unable to take oral therapy during the first 24 hours of their hospital stay (e.g. because of impending endoscopy), these drugs are predominately administered through the intravenous route during their initial period of hospitalization. However, some clinicians allow patients to take oral medication with small amounts of water, and as such oral PPIs and H₂RAs could be used instead of intravenous agents, even as initial therapy.

In contrast to *in vitro* studies, clinical trials evaluating the efficacy of acute administration of H₂RAs and PPIs for upper-GI bleeding have provided mixed results. Many of these studies differ with respect to the route of drug administration, the dosage of drug given and the type of control employed. In addition, many of these clinical trials (most of which were included in this analytical review) have sample sizes that are too small to reliably assess the effect of treatment.

In order to obtain greater statistical power to evaluate the efficacy of both oral and intravenous H₂RAs for the immediate treatment of upper GI hemorrhage, in 1985 Collins and Langman conducted a meta-analysis of 27 available randomized controlled trials (RCTs). Their study revealed that oral and intravenous H₂RAs reduced bleeding, emergency surgical rates and deaths in hospital by approximately 10, 20, and 30%, respectively. However, only the outcomes of surgery and death were found to be statistically significant ($p=0.05$ and 0.02 , respectively).⁷ In 1990, Kenney *et al.* reevaluated the question posed by Collins by adding three recent RCTs to their analysis. Similar reductions in continued bleeding, surgical rates and mortality were demonstrated with a borderline statistical significance.⁸

Although these previous studies provide a general measure of the efficacy of intravenous and oral H₂RAs, they do not exclusively evaluate the efficacy of intravenous H₂RAs in the initial treatment of upper-GI bleeding. This is because RCTs that compared initial treatment with intravenous H₂RAs to initial treatment with intravenous placebo (with both groups usually receiving oral therapy thereafter) were combined with RCTs that compared initial intravenous and subsequent oral H₂RAs with initial intravenous and subsequent oral placebo. Furthermore, these studies do not address the efficacy of other acid-reducing agents such as proton pump inhibitors. Currently, two trials exist which compare the effects of intravenous omeprazole (Losec) against placebo for the acute treat-

This work was carried out at the University of Toronto Program in Clinical Epidemiology and Health Care Research and the Departments of Health Administration and Medicine; Departments of Medicine and Pharmacy at Mount Sinai Hospital and The University Health Network, Toronto, Canada.

This work was supported by a grant from the Faculty of Medicine, University of Toronto.

Akash Ghai was a medical student at the University of Toronto at the time this study was undertaken.

ment of GI hemorrhage. Of these two studies, one by Hasselgren *et al.* demonstrated significant reductions in mortality, surgery and continued bleeding rates while another larger study by Daneshmend *et al.* demonstrated no significant reductions in any of these primary endpoints.^{9,10}

Determining the efficacy of intravenous acid-reducing agents may have important implications with respect to hospital costs and the merits of other potential treatment strategies. Intravenous H₂RAs are commonly used at our institution (Mount Sinai Hospital, Toronto, Canada – a general hospital with 300 acute care beds) and current figures reveal that we spend less than \$25,000/year (Canadian dollars) on these drug – not a terribly large amount. However, intravenous formulations of PPIs (e.g. pantoprazole) will soon be broadly marketed and may greatly increase expenses for most institutions if clinicians switch from intravenous H₂RAs to intravenous pantoprazole (Pantoloc). Thus, conclusive evidence with respect to the efficacy of both intravenous PPIs and H₂RAs may facilitate formulary decision making by either justifying continued use of intravenous therapy or protecting hospitals from larger expenditures without justification. If intravenous acid-reduction treatments are found to be of no significant benefit, other treatment options could be considered more seriously, especially for “stable” patients who are not allowed oral intake simply because they are awaiting endoscopy. One option could be to withhold acid-reduction treatment from such patients until they can begin oral therapy. A second option could be to start oral acid reduction therapy immediately with “sips of water.”

Due to the potential patient management and hospital economic implications, we performed a meta-analysis consisting of all existing data from randomized controlled trials to determine the efficacy of intravenous H₂RAs or PPIs compared with intravenous placebo for the acute treatment of upper GI hemorrhage.

Methods

Literature Search

The MEDLINE (1966-1998), Excerpta Medica (1966-1998), and International Pharmaceutical Abstract (1970-1998) bibliographic databases were used to identify all English-language literature included under the key words *peptic ulcer bleeding, gastrointestinal hemorrhage,*

randomized controlled trials, and *clinical trials* as well as each of the treatments under consideration: *cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid),* and *omeprazole (Losec).* Based on their title and abstract (when available), published articles were retrieved. In addition, a manual search was performed using the references from each retrieved report, review articles, and chapters from textbooks on gastroenterology. Only references published in the English language were considered. The authors of the studies were not contacted to identify additional studies.

Selection Criteria

The following criteria were used to select the studies:

- 1. Randomized controlled trials.
- 2. Trials including only patients presenting with acute upper non-variceal gastrointestinal hemorrhage.
- 3. Studies including interventions with intravenous ranitidine, cimetidine, famotidine, or omeprazole.
- 4. Studies that compared the H₂RA or PPI drug with a placebo.
- 5. Studies which did not endoscopically treat bleeding gastrointestinal ulcers prior to acid-reduction treatment.

Data Abstraction and Classification (Table 1)

The following information was extracted from all the articles that satisfied the inclusion criteria: (1) author and year of study; (2) sample sizes of the experimental and control groups; (3) a description of the interventions in the experimental and control groups; (4) inclusion and exclusion criteria for the sample populations; (5) study outcome measures; (6) the number of events for each outcome evaluated. Data abstraction was performed on two separate occasions by the authors to identify and resolve any discrepancies in the data recordings.

All studies were then divided into two groups based on the method of treatment administration (Table 1). Studies were labeled “primary treatment models” when initial treatment with intravenous H₂RAs or PPIs was directly compared to initial treatment with intravenous placebo. In some of these studies, both treatment arms may also have received subsequent oral therapy. Studies with these treatment models effectively isolate the potential benefit of treatment with early intravenous acid-reduction therapy. Studies were labeled “secondary treatment models” when initial intravenous and subsequent oral H₂RAs and PPIs were compared with various control thera-

Table 1
Primary and Secondary Study Treatment Regimes of Drug Administration

Study Model	Acid Reducing Agent Drug Protocol	Control Protocol	Number of Studies
Primary	H ₂ RA i.v. only	Saline i.v.	5
Primary	H ₂ RA i.v. only	No treatment	1
Primary	H ₂ RA i.v. then H ₂ RA p.o.	Saline i.v. then H ₂ RA p.o.	1
Primary	PPI i.v. then PPI p.o.	Mannitol i.v. then PPI p.o.	1
Secondary	H ₂ RA i.v. then H ₂ RA p.o.	Saline i.v. then saline p.o.	12
Secondary	H ₂ RA i.v. then H ₂ RA p.o.	No treatment	1
Secondary	H ₂ RA i.v. then H ₂ RA p.o.	Nasogastric suction and antacids	2
Secondary	H ₂ RA i.v. then H ₂ RA p.o.	Dicione i.m., Vitamin K i.m., Alugastrin p.o., Calcium gluconate i.v.	1
Secondary	PPI i.v. then PPI p.o.	Saline i.v. then saline p.o.	1

H₂RA – H₂-receptor antagonist, PPI – proton pump inhibitor

studies that did not involve either of these classes of drugs (placebo). Thus, studies with these treatment models evaluate the combined effect of both oral and intravenous acid reduction therapy.

Trial Quality

Two reviewers, blinded to study title, journal, authors and year of publication, independently evaluated the quality of each article's methods using a modified version of a previously developed quality-assessment instrument for randomized controlled trials.¹¹ This 15-item instrument evaluates quality in five areas: selection of study subjects (two items), randomization procedures (three items), description of treatment regimes (two items), blinding procedures (three items), and use of appropriate statistical analyses (five items). Both reviewers were trained in quantitative analytical methods and study design, and neither was previously familiar with the literature related to acid-reducing therapy for gastrointestinal bleeding. When interrater discrepancies in the quality-evaluation existed, they were documented and the reviewers met to resolve them. After agreement was reached, a total quality score was assigned to each article. Two points were assigned for each quality item that was satisfied and one point was assigned for any quality item that was partially satisfied. The sum of the points was calculated to produce a total score. The range of total quality scores for the articles reviewed was 0–30.

Statistical Methods

Continued bleeding, mortality and operation rates were determined to be the primary endpoints of the study. Transfusion requirement was not included as an endpoint, because of a lack of consistency in the measurement of this outcome among the individual trials. For instance, some studies reported the number of patients requiring

transfusions, while other studies reported the total number of transfusion units for each of their study groups.

Each of the three primary endpoints was analyzed separately and in various subgroups. In each analysis, two measures of association – odd ratios (OR) and risk difference (RD) (and their associated 95% confidence intervals [CIs]) – were used to quantify the protective effect of intravenous acid-reducing therapy in “primary” studies and the combined effect of intravenous and oral acid-reducing agents in “secondary” studies. To combine these measures throughout the studies, we calculated summary ORs, summary RDs, and their 95% CIs. We defined the OR as the odds of the outcome in the acid-reduction group divided by the odds of that outcome in the control group. The RD is defined as the proportion having an outcome in the acid-reduction therapy group minus the proportion having that same outcome in the control group.

Both the summary OR and the summary RD are calculated from models in which the observed treatment effect for a study is a combination of the true effect for the individual study and sampling variation. Differences between studies in the observed effect (OR or RD) are used to estimate the study-to-study variation and this variation is incorporated into the estimate of the standard error of the summary measure.

The summary OR was calculated using logistic regression with a dichotomous variable for treatment and a categorical variable for each study. Extra-binomial variation between studies was allowed for thorough estimation of the dispersion parameter from the given data.¹² Where this dispersion parameter was larger than 1.0, the esti-

Table 2
Summary of H₂RA and PPI Primary studies for Acute Upper Gastrointestinal Hemorrhage Treatment

Study	Trial Quality	Treatment Protocol	n	Gastric Ulcers (n)	Duodenal Ulcers (n)	Continued bleeding (n)	Operation need (n)	Death (n)
Hasselgren ¹⁰ (1997)	27	Omeprazole 80 mg i.v. bolus then 8 mg/hr x 72 hrs, then omeprazole 20 mg p.o. x 18 days.	15	88	71	51	4	1
		Mannitol 40 mg i.v. bolus then 8 mg/hr x 72 hrs, then omeprazole 20 mg p.o. x 18 days.	9					
			16	90	73	75	16	1
			3					
Walt ¹⁴ (1992)	22	Famotidine 10 mg i.v. bolus then 3.2 mg/hr i.v. x 72 hrs, then famotidine 40 mg qd until discharge.	49	221	268	119	77	31
		Isotonic saline i.v. bolus then continuous isotonic saline i.v. infusion x 72 hrs, then famotidine 40 mg qd until discharge.	7					
			50	224	277	129	86	25
			8					
Basso ¹⁵ (1986)	26	Ranitidine 300 mg/24 hrs. i.v. x 7 days.	31	8	18	14	8	3
		Continuous isotonic saline i.v. infusion x 7 days.	32	7	17	14	6	4
Coraggio ¹⁶ (1984)	20	Ranitidine 50 mg/4 hrs. i.v. until 12 hrs after first report of clear aspirate.	20	4	6	10	10	0
		No treatment.	20	6	4	13	11	0
Zuckerman ¹⁷ (1983)	22	Cimetidine 300 mg i.v. q6-12h x 72 hrs.	153	20	35	44	NA	10
		Dextrose solution i.v. q6-12h x 72 hrs	132	23	27	30	NA	4
Focco ¹⁸ (1981)	13	Cimetidine 1200 mg i.v. qd x 96 hrs.	10	0	10	1	NA	NA
		Continuous isotonic saline i.v. infusion qd x 96 hrs.	8	0	8	1	NA	NA
Glanz ¹⁹ (1980)	14	Cimetidine 1200 mg i.v. qd x 92 hrs.	18	3	8	0	NA	NA
		Continuous isotonic saline i.v. infusion qd x 92 hrs.	19	5	10	3	NA	NA
Teres ²⁰ (1979)	24	Cimetidine 200 mg i.v. q4h x 48 hrs.	15	NA	NA	10	NA	6
		Isotonic saline 200 ml i.v. q4h x 48 hrs. 12 NA NA 8 NA 4						
		Active Treatment Total	903	355	416	249	99	51
		Placebo Total	894	366	418	273	119	38
		Total	1,797	721	834	522	218	89

NA not available, and n for sample size

mated covariance matrix was multiplied by the parameter. These increased variances were used to calculate Wald confidence intervals which reflect both the within-study and the between-study variances of the estimates. The summary RD was calculated using the random effects method of DerSimonian and Laird.¹³ If the 95% confidence interval for an OR includes 1.0, then the OR is not significantly different from 1.0 at the (=0.05 level. Similarly, if a confidence interval for a RD includes 0.0, then the RD is not significantly different from 0.0 at the (=0.05 level. Both methods incorporate random effects where the variation between studies suggests that random effects are appropriate, that is, where the variation between studies is larger than would be expected under a fixed-effects model.

Before producing the summary measures, we assessed the amount of heterogeneity between individual estimates in order to identify studies that may, due to varying design factors, have resulted in unusually large or small estimates. For the RD analyses, we computed the Q statistic described by DerSimonian and Laird and also examined

contributions of individual studies to this statistic.¹³ For the OR analyses, we computed the likelihood ratio (LR) test comparing a model with a study-by-treatment interaction to a model with a constant treatment effect. We also examined the contribution of each study to the LR statistic. In both types of analyses, a contribution of 3.5 or more to the test statistic or a p-value for the Q or LR test of 0.2 or less was used as an indication of possible heterogeneity and individual studies were examined more closely to ensure their suitability for inclusion in a summary measure.

Subgroup analyses were performed to determine the impact of treatment type (H₂RA vs. PPI) and administration (primary model vs. secondary model) on each of the primary endpoints. However, only the primary studies directly investigate the efficacy of intravenous acid-reduction therapy compared to intravenous placebo for the acute treatment of GI hemorrhage and therefore conclusions about the effectiveness of intravenous acid-reduction agents will rest largely on the results of these primary studies.

Table 3
Summary of H₂RA and PPI Primary studies for Acute Upper Gastrointestinal Hemorrhage Treatment

Study	Trial Quality	Treatment Protocol	n	Gastric Ulcers (n)	Duodenal Ulcers (n)	Continued bleeding (n)	Operation need (n)	Death (n)
Daneshmand ¹¹ (1992)	27	Omeprazole 80 mg i.v. bolus, then 40 mg i.v. q8h x 1 day, then 40 mg p.o. b.i.d. x 3 days. Mannitol i.v. bolus, then mannitol i.v. q8h x 1 day, then placebo 40 mg p.o. b.i.d. x 3 days.	578 569	97 93	149 164	85 100	62 63	40 30
Gray ²¹ (1986)	23	Ranitidine 50 mg i.v. q8h x 3 days followed by then 150 mg p.o. b.i.d. x 7 days until discharge Placebo 50 mg i.v. q8h x 3 days followed by 150 mg p.o. b.i.d. x 7 days until discharge.	50 52	19 22	27 26	8 14	5 8	1 2
Stiel ²² (1984)	22	Cimetidine 200 mg i.v. q6h x 2 days then 200 mg p.o. t.i.d. and 400 mg nocte x 10 days. Placebo 200 mg i.v. q6h x 2 days then 200 mg p.o. t.i.d. and 400 mg nocte x 10 days.	29 26	NA NA	NA NA	5 11	3 4	0 0
Carr-Locke ²³ (1984)	21	Cimetidine 200 mg bolus i.v., then 1200 mg i.v. x 2 days followed by 200 mg p.o. t.i.d. and 400 mg nocte x 7 days. Placebo 200 mg bolus i.v., then 1200 mg i.v. x 2 days followed by 200 mg p.o. t.i.d. and 400 mg nocte x 7 days.	51 54	22 29	29 25	16 15	7 6	NA NA
Darle ²⁴ (1984)	19	Cimetidine 200 mg i.v. q6h x 2-3 days followed by 200 mg p.o. t.i.d. and 400 mg nocte x 2-3 days. Placebo 200 mg i.v. q6h x 2-3 days followed by 200 mg p.o. t.i.d. and 400 mg nocte x 2-3 days.	33 39	10 12	20 23	3 3	1 2	1 5
Birnie ²⁵ (1984)	16	Cimetidine 400 mg i.v. q6h until fit for p.o. then 200 mg p.o. t.i.d. and 400 mg nocte p.r.n. Placebo 400 mg i.v. q6h until fit for p.o. then 200 mg p.o. t.i.d. and 400 mg nocte p.r.n.	106 107	9 6	33 39	16 15	2 7	4 4
Barer ²⁶ (1983)	28	Cimetidine 400 mg i.v. q6h x 48 hrs, followed by 400 mg p.o. q6h x 6 days. Isotonic saline i.v. q6h x 48 hrs, followed by placebo 400 mg p.o. q6h x 6 days.	232 219	65 72	76 60	49 50	32 35	18 23
Nowak ²⁷ (1981)	18	Ranitidine 50 mg i.v. b.i.d. x 48 hrs, then 150 mg p.o. b.i.d. Diclonone 500 mg i.m. t.i.d., Vitamin K 50 mg i.m. t.i.d., 1 tablet of Almagest t.i.d. and 10 ml 10% calcium gluconate i.v. b.i.d.	25 25	10 11	11 7	3 11	1 6	NA NA
Anvanitakis ²⁸ (1981)	13	Cimetidine 200 mg i.v. q4h x 48 hrs, followed by 400 mg p.o. q6h x 5 days. Continuous nasogastric suction followed by liquid antacid (magnesium and aluminum hydroxide) 15 ml q2h x 5 days.	10 9	NA NA	NA NA	1 3	NA NA	NA NA
Carstensen ²⁹ (1980)	22	Cimetidine 200 mg i.v. q4h x 72 hrs, then 200 mg p.o. t.i.d. and 400 mg nocte x 25 days. Isotonic saline i.v. q4h x 72 hrs, then placebo 200 mg p.o. t.i.d. and 400 mg nocte x 25 days.	40 48	15 18	21 25	NA NA	15 16	4 5
Galmiche ³⁰ (1980)	21	Cimetidine 1600 mg/day i.v. x 3 days followed by 200 mg p.o. t.i.d. and 400 mg nocte x 4 days. Continuous 5% glucose solution i.v. infusion x 3 days followed by placebo 200 mg p.o. t.i.d. and 400 mg nocte x 4 days.	46 47	24 24	12 11	5 12	NA NA	NA NA
Meredith ³¹ (1980)	21	Cimetidine 200 mg bolus i.v., followed by 50 mg/hr x 48 hrs then followed by 200 mg p.o. t.i.d. and 400 mg nocte x 10 days. Isotonic saline i.v. bolus then run at 50cc/hr x 48 hrs then followed by placebo 200 mg p.o. t.i.d. and 400 mg nocte x 10 days.	45 43	6 9	21 25	4 2	6 1	1 0
Pickard ³² (1979)	14	Cimetidine 200 mg bolus i.v., then 250 mg q6h x 48 hrs, then 200 mg p.o. t.i.d. and 400 mg nocte x 5 days. Placebo 200 mg bolus i.v., then 250 mg q6h x 48 hrs, then 200 mg p.o. t.i.d. and 400 mg nocte x 5 days.	33 36	4 8	3 15	12 10	NA NA	NA NA
Siddiqi ³³ (1979)	13	Cimetidine 200 mg i.v. q6h x 48 hrs, then 200 mg p.o. t.i.d. and 400 mg nocte x 5 days. No treatment.	58 55	11 14	17 20	NA NA	8 8	4 5
Nair ³⁴ (1979)	11	Cimetidine 300 mg i.v. q6h x 48 hrs, followed by 300 mg p.o. q6h until discharge Continuous nasogastric suction x 48 hrs, followed by antacids q2h until discharge	14 15	8 8	3 4	NA NA	NA NA	0 4
Dykes ³⁵ (1978)	18	Cimetidine 200 mg i.v. q4h x 48 hrs, followed by 200 mg p.o. t.i.d. and 400 mg nocte x 7 days 5% dextrose solution i.v. q4h x 48 hrs, followed by placebo 200 mg p.o. t.i.d. and 400 mg nocte x 7 days. 41 16 11 14 NA NA	41	9	18	8	NA	NA
Kang ³⁶ (1978)	16	Cimetidine 200 mg i.v. q4h x 48 hrs, followed by 400 mg p.o. q6h x 7 days. Placebo 200 mg i.v. q4h x 48 hrs, followed by 400 mg p.o. q6h x 7 days.	32 33	5 16	15 9	7 13	NA NA	NA NA
Active Treatment Total			1,423	324	474	222	142	73
Placebo Total			1,418	367	482	273	156	78
Total			2,841	691	956	95	298	151

NA not available, and n for sample size

relationship between the assessed quality of studies and the estimated effectiveness of the treatment, we performed a sensitivity analysis. With a threshold set first at the lowest quality score and subsequently at each higher observed score, we calculated summary odds ratios and confidence intervals only for studies that met or exceeded the threshold.¹¹

Results

Using our 5 selection criteria, 25 of the 31 studies found in the literature were included in the meta-analysis.^{9,10,14-36} Three studies were excluded because the studies compared oral treatment versus oral placebo.^{3,35,36} Two other studies were excluded because the method of therapy administration was not defined.^{40,41} One recent study was excluded because endoscopic therapy was given to some patients before they received either intravenous omeprazole or intravenous placebo and the endoscopic treatment distribution between the active treatment and placebo groups was not available.⁴²

Primary Studies (Table 2)

A total of eight of the twenty-five studies (32%) met the criteria for being primary studies (Table 2). Seven of these studies compared intravenous H₂RAs with placebo and one study compared intravenous omeprazole with placebo. In every study, diagnostic endoscopy was performed for either the majority or all patients within 1 to 24 hours after hospital admission.

Reported end points varied among trials. However, most studies reported three major endpoints: continued bleeding, operation need, and mortality. With respect to the H₂RA studies, a total of 1,475 patients were present in the H₂RA and placebo groups. None of these studies were able to demonstrate a significant decline in continued bleeding rates resulting from treatment with intravenous H₂RAs. Studies that included mortality and need-for-surgery as outcome measures showed similar event rates in both groups. A study

by Hasselgren *et al.* compared intravenous omeprazole (n=159) to intravenous placebo (n=163) and demonstrated significant reductions in continued bleeding (p=0.004) and operation need (p=0.003). However, twenty patients in this study had also undergone therapeutic endoscopy prior to treatment with omeprazole.⁹

Secondary Studies (Table 3)

The literature search revealed seventeen secondary studies comparing intravenous and oral acid-reduction agents to various control therapeutic strategies (Table 3). Information from these studies was utilized to provide additional evidence for the efficacy of acid-reduction therapy and as a comparative measure to results from the primary group of studies. Sixteen of these studies compared intravenous and oral H₂RAs with a control (1,694 patients) and one study compared intravenous and oral omeprazole with a control (1,147 patients). In every study, diagnostic endoscopy was performed for either the majority or all patients within 1 to 48 hours after hospital admission.

Only two of the seventeen studies demonstrated a significant reduction in any of the three primary end points when compared to controls. A study by Nowak *et al.* demonstrated a significant reduction (p<0.05) in the incidence of both GI bleeding and operation need for a cohort treated with ranitidine.²⁷ Another study by Barer *et al.* showed a significant decline (p=0.045) in mortality for a cohort treated with cimetidine.²⁶

Meta-Analysis

Tables 4, 5 and 6 list the summary odds ratios, risk differences (and their associated 95% CIs), Q statistics and LR for each of the three primary outcomes within the various study groups.

Continued Bleeding (Table 4)

The proportion of patients in whom bleeding was judged to have been persistent ranged from 0 percent¹⁹ to 67 percent²⁰ among all tri-

Table 4
Summary OR and 95% CIs for Continued Bleeding

Groups	Continued Bleeding					
	OR (95% CI) [†]	LR [‡]	p Value	RD (95% CI) [†]	Q statistic [§]	p Value
Primary studies	0.859 (0.667 to 1.105)	11.4*	0.093	-0.021 (-0.066 to +0.024)	8.8	0.211
Secondary studies	0.762 (0.603 to 0.964)	18.6*	0.137	-0.020 (-0.063 to +0.023)	17.4*	0.180
All studies	0.807 (0.681 to 0.955)	30.6*	0.066	-0.018 (-0.049 to +0.013)	25.4*	0.196
H ₂ RA primary studies	0.968 (0.771 to 1.216)	6.8	0.315	-0.006 (-0.049 to +0.038)	3.9	0.659
H ₂ RA secondary studies	0.733 (0.536 to 1.00)	18.4*	0.105	-0.028 (-0.083 to +0.026)	17.3*	0.139
H ₂ RA studies	0.852 (0.696 to 1.043)	27.6*	0.077	-0.015 (-0.051 to +0.022)	21.9	0.258
Omeprazole studies (primary and secondary)	0.714 (0.504 to 1.011)	1.8*	0.179	-0.022 (+0.087 to -0.044)	1.8*	0.180

* Possible heterogeneity within the study group based on a p value of less than 0.20 from the Q statistic or LR test

† Odds ratios with confidence intervals (CIs) that overlap 1.0 and risk differences with CIs that overlap 0 are not statistically significant at p = 0.05.

‡ Test for heterogeneity for the odds ratio analysis.

§ Test for heterogeneity for the risk difference analysis.

als. This presumably reflects differences in the types of patients studied and the criteria used to define this end point. Continued bleeding occurred less frequently for patients treated with acid-reduction therapy in 14 of 22 trials which reported this outcome.^{9,10,14,16,18,19,21,22,26-28,30,35,36} However, a statistically significant result ($p<0.05$) was only noted in one study.²⁷

The LR and Q statistic tests demonstrated that studies by Hasselgren, Nowak and Zuckerman significantly ($p<0.20$) contributed to the heterogeneity found in the primary, secondary and combined study groups.^{9,17,27} However, on closer inspection, it was determined that these studies did not possess any variance in design factors that could preclude them from inclusion in the summary measures.

Examination of the 8 primary studies which directly evaluate the efficacy of intravenous acid-reducing agents revealed a statistically insignificant summary OR of 0.859 (95% CI = 0.667–1.105) and a RD of -0.021 (95% CI = -0.066–0.024). However, results from 14 trials in the secondary study group which reported this outcome demonstrated a lower OR of 0.762 (95% CI = 0.603–0.964) which was statistically significant. Combining these two study groups (22 trials) produced a statistically significant OR of 0.807 (95% CI = 0.681–0.955), and RD of -0.018 (95% CI = -0.049–0.013).

Need for Surgery (Table 5)

Surgery was performed in 1.9 percent to 55 percent¹⁶ of patients in the 15 studies in which it was reported; it was less common in the treatment group than in control group in 12 of these studies.^{9,10,14,16,21,22,24-27,29,33} Only one study noted a statistically significant reduction in the need for surgery in the active treatment group.²⁷

Both the Q statistic and the LR test revealed heterogeneity in the combined and primary study groups originating from studies by Hasselgren, Nowak and Meredith.^{9,27,31} On closer inspection of these studies, it was determined that they did not possess any variance in

design factors that would preclude them from inclusion in the summary measures.

Grouping together the 4 primary studies which reported surgical outcomes resulted in an insignificant summary OR of 0.817 (95% CI = 0.527–1.267) and a corresponding RD of -0.037 (95% CI = -0.071–0.004). Combining the 11 secondary studies which reported this end point yielded a higher OR of 0.895 (95% CI = 0.685–1.120) and a smaller RD of -0.014 (95% CI = -0.038–0.009). Combining the primary and secondary study groups (15 trials) yielded an OR of 0.862 (95% CI = 0.693–1.073) and a RD of -0.019 (95% CI = -0.039–0.002), both values statistically insignificant.

Death (Table 6)

Death rates for the treatment group ranged from 0 percent^{16,22,31,34} to 40 percent.³⁰ In the 16 studies that reported data for this end point, 7 studies had lower death rates in the treatment group than in the control group.^{15,21,24,26,29,33,34}

The LR and Q statistic tests did not reveal any significant heterogeneity in the primary, secondary and combined study groups.

Grouping together the 6 primary studies that reported mortality as an outcome yielded a statistically significant summary OR of 1.336 (95% CI = 1.066–1.676) but an insignificant RD of +0.007 (95% CI = -0.008–0.023). Summary OR and RD for the 10 trials in the secondary study group that reported this outcome were found to be smaller at 0.901 (95% CI = 0.627–1.294) and -0.001 (95% CI = -0.020–0.017), respectively. Combining all studies (16 trials) yielded an OR of 1.038 (95% CI = 0.803–1.343) and a RD of 0.004 (95% CI = -0.008–0.016), both values statistically insignificant.

Quality-Based Sensitivity Analysis (Figures 1, 2 and 3)

Analysis of the sensitivity of the results to trial quality scores revealed some interesting trends. The elimination of trials with poor quality

Table 5
Summary OR and 95% CIs for Operation Need

Groups	Operation Need					
	OR (95% CI) [†]	LR [‡]	p Value	RD (95% CI) [†]	Q statistic [§]	p Value
Primary studies	0.817 (0.527 to 1.267)	7.0*	0.030	-0.037 (-0.071 to +0.004)	6.0*	0.050
Secondary studies	0.895 (0.685 to 1.170)	12.8	0.235	-0.014 (-0.038 to +0.009)	10.0	0.448
All studies	0.862 (0.693 to 1.073)	20.0*	0.095	-0.019 (-0.039 to +0.002)	16.0*	0.248
H ₂ RA primary studies	0.927 (0.769 to 1.116)	0.7	0.414	-0.011 (-0.055 to +0.033)	0.7	0.416
H ₂ RA secondary studies	0.844 (0.581 to 1.225)	12.5*	0.186	-0.020 (-0.052 to +0.012)	9.7*	0.378
H ₂ RA studies	0.886 (0.704 to 1.116)	13.4	0.270	-0.018 (-0.044 to +0.007)	10.5	0.487
Omeprazole studies (primary and secondary)	0.809 (0.347 to 1.886)	6.5*	0.011	-0.011 (-0.062 to +0.040)	5.5*	0.020

* Possible heterogeneity within the study group based on a p value of less than 0.20 from the Q statistic or LR test.
† Odds ratios with confidence intervals (CIs) that overlap 1.0 and risk differences with CIs that overlap 0 are not statistically significant at $p = 0.05$.
‡ Test for heterogeneity for the odds ratio analysis.
§ Test for heterogeneity for the risk difference analysis.

Table 6
Summary OR and 95% CIs for Mortality

Groups	Mortality					
	OR (95% CI) [†]	LR [‡]	p Value	RD (95% CI) [†]	Q statistic [§]	p Value
Primary studies	1.336 (1.066 to 1.676)	1.3	0.854	+0.007 (-0.008 to +0.023)	1.2	0.863
Secondary studies	0.901 (0.627 to 1.294)	15.0	0.133	-0.001 (-0.020 to +0.017)	8.3	0.599
All studies	1.038 (0.803 to 1.343)	18.3	0.247	+0.004 (-0.008 to +0.016)	10.9	0.760
H ₂ RA primary studies	1.346 (1.045 to 1.733)	1.3	0.727	+0.016 (-0.007 to +0.040)	1.1	0.739
H ₂ RA secondary studies	0.638 (0.417 to 0.987)	10.2*	0.332	-0.015 (-0.040 to +0.009)	4.7*	0.860
H ₂ RA studies	0.934 (0.682 to 1.278)	16.8	0.207	+0.001 (-0.016 to +0.018)	9.7	0.718
Omeprazole studies (primary and secondary)	1.325 (1.213 to 1.448)	0.03	0.854	+0.005 (-0.010 to +0.019)	0.034	0.854

* Possible heterogeneity within the study group based on a p value of less than 0.20 from the Q statistic or LR test.

† Odds ratios with confidence intervals (CIs) that overlap 1.0 and risk differences with CIs that overlap 0 are not statistically significant at p = 0.05.

‡ Test for heterogeneity for the odds ratio analysis

§ Test for heterogeneity for the risk difference analysis.

scores from the primary study group resulted in a decreasing OR (greater therapeutic effect) and widening 95% CI for both the endpoints of continued bleeding and need for surgery (Figure 1 and 2). For the mortality endpoint, removing poor-quality studies had the effect of decreasing the OR (lesser therapeutic harm) and narrowing the 95% CI (Figure 3).

Withdrawal of poor-quality studies from the secondary study group had the effect of increasing the summary OR (lesser therapeutic effect) and narrowing the 95% CI for the continued bleeding and need-for-surgery outcomes. For the mortality endpoint, withdrawal of poor quality studies from the secondary study group had the effect of gradually increasing the OR (greater therapeutic harm) and widening the 95% CI.

Combining both study groups had the effect of negating the observed trends between the summary OR and the trial quality score.

Discussion

The goal of this meta-analysis was to evaluate the efficacy of intravenous acid-reduction therapy for the initial treatment (i.e. first few hours or days) of non-variceal upper gastrointestinal hemorrhage. Meta-analysis, which takes a more structured approach to literature identification and synthesis than the traditional narrative review, often provides a means to answer important clinical questions that individual studies cannot answer definitively.^{43,44} This analytical method seemed particularly well suited to assess the efficacy of the intravenous acid-reducing agents, since there is variation in the magnitude and direction of effects from individual clinical trials.

In contrast to previously published reviews of acid-reduction therapy for acute GI hemorrhage, this meta-analysis differed in two major ways. First, we included the latest randomized controlled trials that evaluated newer agents such as famotidine and omeprazole.

Compared to older trials, these recent studies have larger sample sizes, which greatly augment the total sample number of our meta-analysis. This larger sample size increases the study's power to determine the value of acid-reduction therapy. In addition, these newer studies also have higher trial-quality scores, which improve the accuracy of the results from the meta-analysis. Secondly, we grouped the studies in a different way to address a new question regarding acid-reduction therapy. Unlike previous works, our goal was to determine exclusively the efficacy of intravenous administration of acid-reduction agents for the initial treatment of upper gastrointestinal hemorrhage. We therefore grouped studies based on primary and secondary treatment models. Studies in the primary group, because they directly evaluated only initial intravenous acid-reduction therapy, provided direct information to answer our inquiry. Studies in the secondary treatment model, while they did not exclusively evaluate intravenous acid-reduction therapy, did provide information on the combined effects of both intravenous and oral preparations of these drugs.

Our data demonstrate two conflicting trends concerning the efficacy of intravenous acid-reduction therapy. First, they demonstrate a slight, though insignificant, trend favoring intravenous acid-reduction treatment for decreasing the incidence of continued bleeding and the need for surgery. Odds ratios for every study group (e.g. primary, secondary, H₂RA-only etc.) were less than 1.0 for both the continued bleeding and operation-need outcomes. However, the confidence intervals for most of these study groups overlapped 1.0, making these values insignificant. An exception is the results for the continued bleeding outcome in the secondary and combined study groups, where the confidence intervals did not overlap 1.0. However, these study groups contain many trials with poor quality scores that, if removed, would yield a minimal and insignificant effect with regard to treatment.

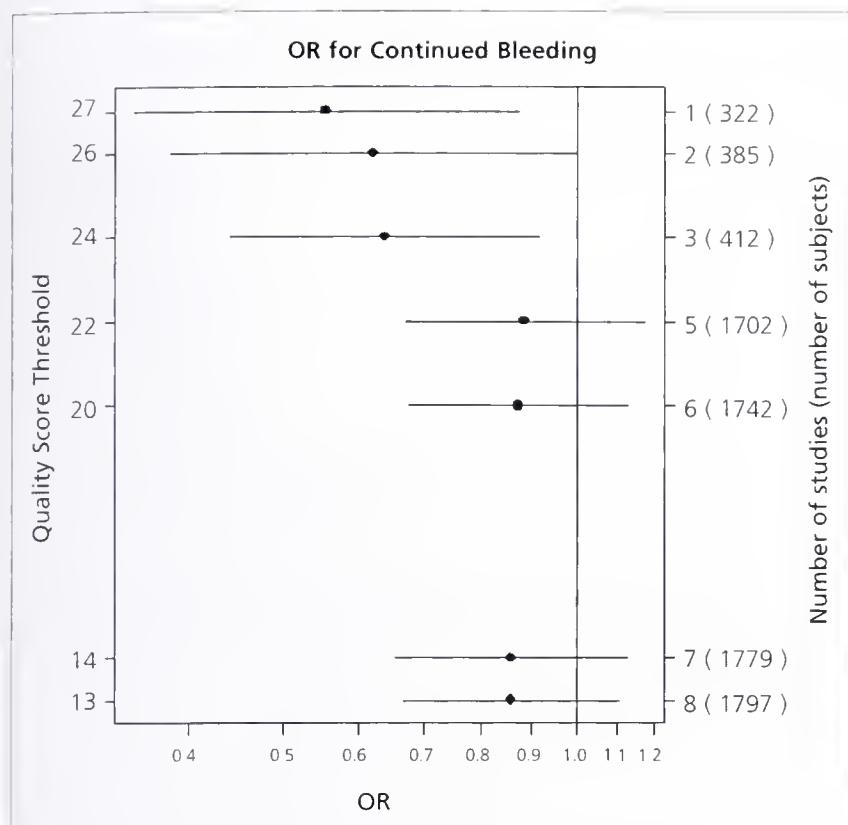


Figure 1. Sequential quality-impact plot examining the impact of trial quality assessment on the summary odds ratios and associated 95% confidence intervals for the continued-bleeding end point in the Primary Study Group. Summary OR with CIs that overlap 1.0 are not statistically significant at $p = 0.05$.

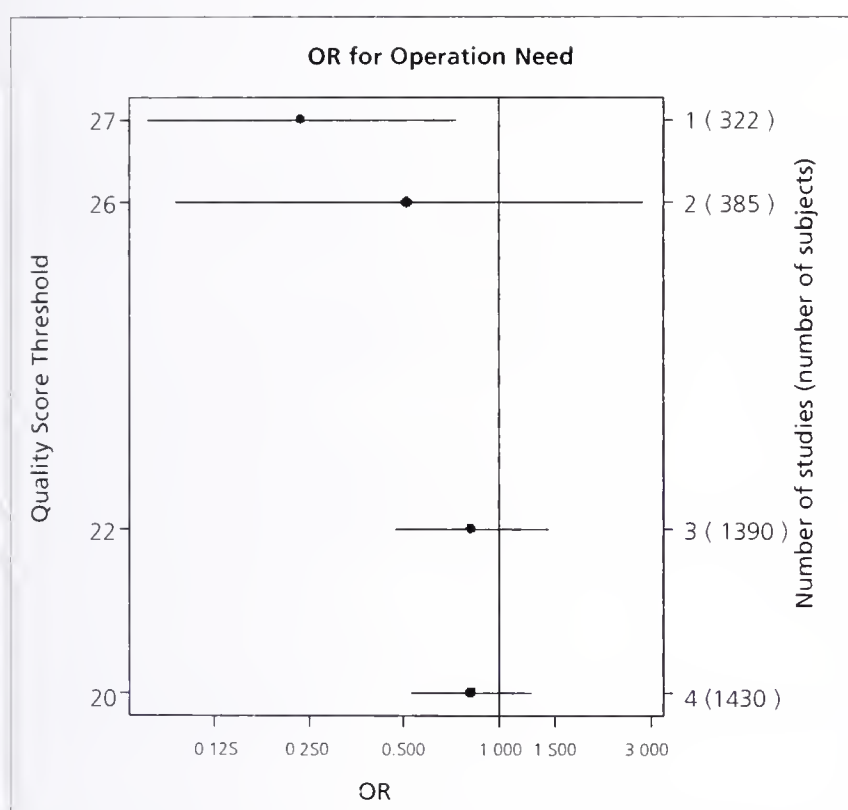


Figure 2. Sequential quality-impact plot examining the impact of trial quality assessment on the summary odds ratios and associated 95% confidence intervals for the surgery-need end point in the Primary Study Group. Summary OR with CIs that overlap 1.0 are not statistically significant at $p = 0.05$.

Second, data from the primary and PPI study groups demonstrate a trend towards an increased risk of death for patients who receive acid-reduction treatment. While the primary study group demonstrated a significantly high OR for mortality, removal of trials with poor quality scores decreased the summary OR and narrowed the 95% CI. Conversely, studies in the secondary study group demonstrated a summary OR of less than 1.0. Removing poor quality studies from this group increased the OR closer to 1.0. Hence, examining the highest quality studies in both the primary and secondary study groups demonstrates that acid-reduction therapy has a minimal

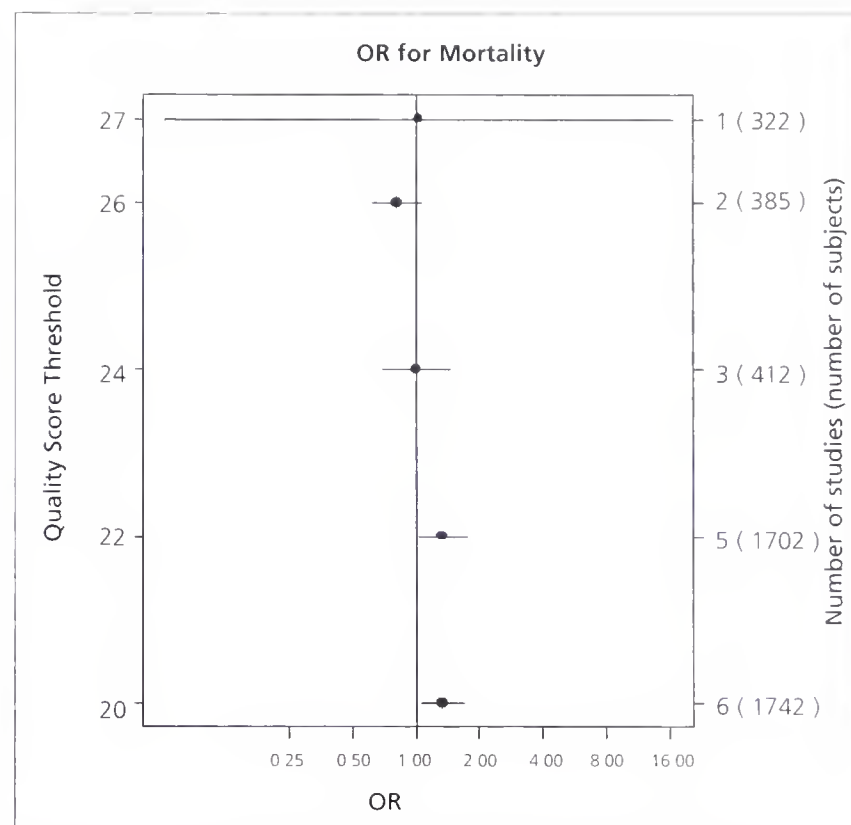


Figure 3. Sequential quality-impact plot examining the impact of trial quality assessment on the summary odds ratios and associated 95% confidence intervals for the mortality end point in the Primary Study Group. Summary OR with CIs that overlap 1.0 are not statistically significant at $p = 0.05$.

effect on mortality. It is plausible that the increased mortality risk in the primary group is a chance event.¹⁴

Results from *in vitro* studies and some clinical trials suggest that intravenous PPIs may be more efficacious than intravenous H_2 RAs for the initial treatment of upper gastrointestinal bleeding.⁴⁵⁻⁴⁹ However, our study could not conclusively demonstrate any advantage of intravenous PPIs over intravenous H_2 RAs for the treatment of upper gastrointestinal bleeding, a finding that is supported by two recent individual trials which directly compared both types of therapy.^{50,51} Comparing the OR for the continued-bleeding and surgery end-points between the omeprazole study group and the H_2 RA primary study group revealed a lower OR for the former group. However, because of the relatively few PPI studies in existence, our meta-analysis lacks the power to reveal any significant differences in effect between these two types of intravenous acid-reducing agents. Looking at these studies individually, Hasselgren *et al.* did demonstrate a significant decline in event rates for each of the primary end points for the omeprazole-treated group. However, a much larger study by Daneshmend *et al.* failed to demonstrate any significant benefit for PPI usage in each of the primary endpoints. In fact, this study demonstrated a trend towards an increased risk of death for the omeprazole-treated group. Thus, we cannot conclude at this time that intravenous PPIs are more efficacious than intravenous H_2 RAs for the immediate treatment of upper non-variceal gastrointestinal bleeding.

We can conclude, however, based on the primary analysis aimed at answering our specific question, that intravenous acid-reduction therapy, when given immediately to patients with acute upper gastrointestinal bleeding prior to the institution of oral antisecretory therapy, may not provide any clinically significant protection against the incidence of continued bleeding, surgery need or mortality. While none of the trials in this meta-analysis examined the efficacy of intravenous pantoprazole, one could infer that since current intravenous acid-reduction agents have not been proven effective in the treatment of gastrointestinal bleeding, a stronger medication such as pantoprazole may also prove to be ineffective. Therefore, if the cost of providing

endoscopic therapy during the initial treatment of acute GI bleeds is not dramatically different. When intravenous PPIs such as pantoprazole are administered widely, hospital-based clinicians may want to think carefully about which kinds of patients will receive them. For those who do not receive the use of intravenous PPIs, the onus is on them to demonstrate its effectiveness in a similar style to our “primary” treatment models (i.e. comparing treatment with intravenous placebo or H₂RAs) with respect to clinically meaningful end points.

We recognize that the majority of the studies in our meta-analysis are over ten years old and that during that time the standard of care has changed to include acute endoscopic therapy. Two meta-analyses have reported a survival advantage for endoscopic therapy when compared to conservative treatment.^{52,53} However, the issue of the efficacy of intravenous acid-reduction therapies remains important because most clinicians still use these intravenous medications in the initial management of upper GI bleeding prior to therapeutic endoscopy, and this has consequences on hospital expenditures for these drugs.

We therefore contend that for patients who are hemodynamically stable, without ongoing hematemesis or other evidence of continued bleeding, clinicians may wish to give oral medication as initial treatment while the patient awaits endoscopy. Khuroo *et al.* did demonstrate a significant benefit of high-dose oral omeprazole for patients with peptic ulcer bleeding.³⁹ In addition, a study from Santos *et al.* demonstrated no significant difference between oral and intravenous ranitidine for the treatment of acute nonvariceal upper GI bleeding.⁵⁴ Thus the use of oral instead of intravenous medication may even facilitate very early discharge in those patients with minor GI bleeding. We suggest that a randomized trial of immediate oral PPIs versus initial intravenous PPIs followed by oral PPIs (as opposed to initial placebo versus initial intravenous PPIs) is warranted. In addition, a trial comparing an intervention of appropriate therapeutic endoscopy coupled with acid suppression (with or without intravenous administration) is also needed.

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Oral Contraceptive-Induced Thrombogenesis: A Review

Andrea K. Boggild, M.Sc. (OT3)

Yael Friedman, M.Sc. (OT3)

Abstract

Since their emergence in the early 1960s, oral contraceptives have been associated with vascular thrombotic events. Numerous investigations over three decades have established a clear link between the ethinylestradiol component of pills and deep vein thrombosis and subsequent pulmonary embolism. Oral contraceptives with $>50\ \mu\text{g}$ ethinylestradiol have been shown to damage vascular intima, impair venous flow, and create a hemostatic profile that favours coagulation, all of which can culminate in thrombus formation. While more recently developed oral contraceptives ($<35\ \mu\text{g}$ ethinylestradiol) also increase procoagulatory factors, they, at the same time, enhance the activity of anticoagulatory pathways. Thus, a situation that tips the hemostatic scale in favour of thrombus formation is thought to occur in low-dose oral contraceptive users who have other identifiable risk factors for clot formation. Such factors include, but are not limited to, obesity, immobility, family history of deep vein thrombosis, rheumatic heart disease, factor V Leiden mutation, increased age, hypertension, and smoking. This paper undertakes to review the epidemiology of oral contraceptive-induced vascular events and the mechanisms by which hemostatic factors are affected by oral contraceptives.

Introduction

It has long been recognized that a correlation exists between oral contraceptive use and vascular disturbance. In 1961, a general practitioner by the name of Dr. Jordan noted this association after his patient, a 40-year-old woman being treated with an estrogen derivative for endometriosis, developed a pulmonary embolism.¹ The relationship between estrogen and thromboembolic events was further substantiated in 1967 by a compelling report published by the Royal College of Practitioners.² Since then, a plethora of studies regarding the etiology and occurrence of thromboembolism in women receiving exogenous estrogen have emerged. Although estrogen derivatives are administered to women for a number of reasons, as in post-menopausal hormone-replacement therapy, the discussion herein will be limited to exploring thromboembolic events in relation to oral contraceptive (OC) use.

Most OCs on the market today are multiphasic and “combined” in that they contain both an estrogen and progesterone/progestogen

component.³ The original OCs or “first-generation” pills were comprised of $>50\ \mu\text{g}$ (high-dose) estradiol plus a varying dose ($0.5 - >1.0\ \text{mg}$) progesterone substituent, which was usually a derivative of nortestosterone such as norethisterone or lynestrenol. In the late 1960s, second-generation pills appeared on the market containing the nortestosterone derivative levonorgestrel coupled to $30\text{--}40\ \mu\text{g}$ of ethinylestradiol (EE). More recently, the third generation of OCs was developed for the purpose of reducing androgenic side effects (such as hirsutism) associated with the progesterone derivatives used in earlier generation pills.⁴ A decrease in androgenicity of third-generation pills can be attributed to a greater affinity of the third generation progestins for the progesterone receptor over other receptors in the steroid family.⁵ Desogestrel, gestodene, and norgestimate are all derived from levonorgestrel and coupled to $30\ \mu\text{g}$ ethinylestradiol in multiphasic, combined preparations. Colloquially, second and third-generation pills are referred to as “low-dose” combined oral contraceptives (COCs). Pill combinations containing less than $50\ \mu\text{g}$ estrogen have been associated with significantly fewer venous and non-venous deaths than their high-dose counterparts.^{6,7} A reduction in estrogen content by 50% leads to a reduction in complication rate by 70%.⁸ Along with other evidence that has amassed since the mid-70s, this supports Dr. Jordan’s association of estrogen with venous thromboembolism (VTE). Although estrogen increases the risk of both arterial and venous events, progestogen confines its effects to arterial disease; most notably in the form of cerebrovascular accidents (CVA/stroke) and myocardial infarctions (MI).⁷ The dose-dependent increase in risk of venous events is typically manifested in the form of deep vein thrombosis (DVT), proximal vein thrombosis (PVT), or pulmonary embolism (PE).⁷

The impact of COCs on blood clotting has been historically evaluated by two different methods.⁹ Many researchers, using retrospective and prospective epidemiological studies, collect information about the incidence of thrombotic events in women using birth control pills. Conversely, specific blood profiles, which reveal coagulation factor and platelet status, are also widely employed and assessed in both COC users and non-users. While the former method allows for generalization of relative risk and is really more instrumental in establishing public health policy, the latter confers upon researchers the opportunity to more thoroughly investigate the effects of COC use and pinpoint the cause of thrombotic events. Although each technique is vastly different in its approach, both methods have contributed substantially to our state of understanding surrounding this phenomenon.

*Correspondence should be addressed to andrea.boggild@utoronto.ca

Epidemiology of COC-Related Vascular Disturbance

Currently, 10 million American women rely on OCs for birth control.^{10,11} In Canada, 21% of women aged 15-39 reported using oral contraceptives in 1994.¹² The highest rate of birth control pill use was found amongst the 20-24 age group at 38%.¹² Worldwide, the number of oral contraceptive users is estimated to be 60 million.¹³ From 1989-1993, the World Health Organization (WHO) conducted a multi-national, hospital-based study, including 769 VTE cases and 1979 age-matched controls. It was concluded that the risk of VTE is 3-4 times higher in OC users than in non-users.¹⁴ In a similar study, it was estimated that the risk of DVT (for all brands of low-dose OCs) is 30-40 per 100,000 women per year exposed, while in non-users, the risk is 5-11 per 100,000 woman-years.⁵ It has also been concluded that VTE occurs more frequently within the first year of OC use and in first time users.^{4,15} Interestingly, second-generation pills carry a DVT risk of only 10-20 per 100,000 woman-years, indicating that the progesterone component may play a role in thrombogenicity.⁵ This assertion was further supported by a study of 80 cases of non-fatal VTE in which the risks associated with levonorgestrel (2nd generation), desogestrel (3rd generation), and gestodene (3rd generation), were 16.1, 29.3, and 28.1 per 100,000 woman-years respectively.¹⁵ It was further concluded that VTE among first time users occurs twice as often with third-generation preparations than with second-generation COCs.¹⁵ Ultimately, these statistics suggest that somewhere between 10-40 cases of non-fatal DVT per 100,000 women using low-dose OCs can be expected annually.⁴ Fortunately, the case fatality rate for VTE is low, with only 1-2% of thrombotic incidences resulting in death.^{5,14}

The WHO has further reported on an additional multi-centre hospital-based, case-control study on OC usage and the risk of stroke, acute MI, and VTE in Africa, Asia, Europe, and Latin America.¹⁶ It was determined that VTE is the most common adverse cardiovascular effect associated with COC use in Europe, while in the developing world, stroke predominates.¹⁶ Unfortunately for OC users of disenfranchised nations, strokes carry a case fatality rate of 5-10%, which is a 5-fold increase over the rate for VTE.¹⁶ As previously mentioned, both estrogen and progesterone are positively correlated to death from non-venous causes such as CVA and MI.⁷ For non-fatal MI in women aged 30-39, the US hospital admission rate is 2.1 per 100,000 non-users, versus 5.6 per 100,000 for users.⁸

Although the risk of DVT is greatly elevated in third-generation pill users (over second-generation and non-users), the risk of MI (arterial disturbance) appears to be diminished with desogestrel or gestodene-containing preparations.^{5,15} A possible explanation for this observation is a decrease in pill androgenicity, which is usually associated with arterial disease. Based on the greater incidence of stroke in the developing world users, it can be speculated that they, unlike European women (who tend to develop DVT more often), have not been introduced to the very recent (c. 1990) third-generation COCs.

Specific Effects of COCs

There are three sets of circumstances necessary for thrombus formation: 1) damage to the intimal lining of a vessel, 2) impaired blood flow, and 3) hypercoagulability.⁸ Each of these phenomena is governed by its own set of factors and affected by different variables such as smoking and exercise. High-dose, first-generation OCs have been found to influence each of the aforementioned situations. Both intimal proliferation of the vascular wall¹⁷ and increased venous distensibility resulting in venous stasis¹⁸ have been associated with

oral contraceptive use. OC use has also been linked to either an increase or decrease in a multitude of both coagulation and fibrinolytic factors. Changes in hemostatic variables however, are less pronounced during use of low-dose pills than in older preparations.^{19,20} It has recently been concluded that plasma levels of most hemostatic variables are altered by COC use^{20,21} (Table 1).

Table 1
Summary of The Major Hemostatic Factors
that are Affected by COCs

Abbreviations: C4B-BP (C4B binding protein); APC (activated Protein C); vWF (von Willebrand Factor); PAI-1 (Plasminogen Activator Inhibitor).

	Increase	Decrease
Anticoagulant Factors	Protein C alpha-2 antitrypsin	Protein S, C4B-BP APC, antithrombin
Procoagulant Factors	Fibrinogen, Prothrombin Factors VII, VIII, IX, X, XI, vWF	
Profibrinolytic Factors	Plasminogen, Factor XII Prokallikrein	t-PA, u-PA
Antifibrinolytic Factors	Factor XIII	PAI-1, Tetranectin

From this table, a general pattern seems to emerge. While changes in coagulation variables appear undesirable in that anticoagulatory proteins are reduced while procoagulatory proteins are increased, fibrinolytic changes show a positive trend through an increase in potency.²⁰

The increase in clotting factors alone is not indicative of a functional hypercoagulability for several reasons. First, clotting factors typically exist in plasma in their proenzyme or inactive state. Furthermore, all clotting factors can be found under normal physiological conditions in concentrations exceeding what would be required of them in the event of coagulation. Factor VIII for instance, exists in varying fractions (60-200%) of its "normal" concentration even though only 25% is required to maintain homeostasis.⁸ Finally, there is no evidence to support that infusing factors in their proenzyme state precipitates a thrombogenic event.⁸ Functional activity of the hemostatic system must therefore be ascertained by evaluating more than just clotting factor concentration.

Indeed, fibrinopeptide A, which is cleaved off during the conversion of fibrinogen to fibrin, is an accurate measure of coagulation activation. It was found that after administration of 30-35 µg EE/gestodene-containing COCs to women, this peptide compound increased by 96%.²²⁻²⁵ A more rapid turnover of fibrinogen to fibrin has also been noted among OC users.²⁶ In addition, the prothrombin fragment 1 + 2 (F 1 + 2), demonstrative of active thrombin formation, increases by 45% after administration of 30-35 µg EE plus desogestrel, gestodene, or norgestimate.²⁷⁻²⁹ Interestingly, a study of 30 women subjected to nine cycles of EE/gestodene OCs confirmed that thrombin generation did not reach the critical concentration necessary to stimulate platelet activation.²² In further support of this finding, plasma concentrations of platelet activation indicators such

Factor VII clotting activity/Factor VII antigen ratio is yet another marker of hypercoagulability. In the 2000 women receiving nine cycles of third-generation OCs, both variables were found to increase.²² The enhancement of Factor VII clotting activity² illustrates that an increase in functional Factor VII (not merely the proenzyme) occurs during OC use.

Activity of the anticoagulatory pathway is also enhanced during OC treatment, as evidenced by the increase in plasma concentration of the protein C-antithrombin complex by 71%.³³ Protein C cleaves active factor V and VIII to an inactive state, and antithrombin antagonizes thrombin, thereby inhibiting clot formation. Fibrinolysis is also activated in women taking OCs. Increases in plasmin by 66% and fibrin degradation products (FDPs) such as D-dimer by 64% have also been observed during COC use.²⁷⁻²⁹ As FDPs are chronically increased, it is supposed that the coagulation system and in turn, the fibrinolytic system, are functionally operative throughout administration of COCs.²⁰ Moreover, plasminogen levels and activity are higher in users than in non-users.²² It has been postulated that this increase may be attributable to decreased levels of a histidine-rich glycoprotein during OC use.^{22,34} Under normal circumstances, this HIS-rich glycoprotein binds to high affinity lysine-binding sites on plasminogen, thus interfering with the association of plasminogen and fibrin.³⁴ Without such interaction, plasmin generation and subsequent activity cannot occur. So, in the absence of HIS-rich glycoprotein, plasminogen is converted to plasmin, and fibrinolysis proceeds. Conceivably, as coagulation precedes fibrinolysis, increased fibrinolytic activity may be a mechanism compensatory to the increased risk of clotting posed by augmented levels of factor VII and fibrinogen,³⁴ along with concomitant decrease in antithrombin III. After all, high factor VII clotting activity along with increased fibrinogen levels has been an accurate sign of impending heart disease and cardiovascular-related death.²¹

Progestogens are believed to have very little influence on hemostatic variables even though more pronounced effects of desogestrel relative to gestodene have been proposed for factor X and protein S levels.²⁰ Estrogen is most highly correlated to levels of factors VII, VIII, IX, and X, as well as antithrombin and plasminogen.³⁵ Although the synthesis and release of coagulation factors are the proposed targets of OCs, changes in concentrations of u-PA, t-PA, and PAI-1 are believed to be affected by COCs through clearance.³⁶ Clearance can be enhanced by increasing the number of cell surface receptors for a given ligand, which can be under hormonal control.³⁷ Coagulation is further promoted by metabolic changes induced by COC use. Oral contraceptives have been associated with elevated levels of plasma VLDLs and chylomicrons.³⁸ It is believed that these highly negative lipoproteins interact with factor XII, thereby facilitating its conversion to an active conformation.^{3,22}

Within the past few years, researchers have begun to investigate the effects of very low-dose OCs (EE=20 µg) on hemostatic variables. In one particular study, 67 women were treated with either a 30 or 20 µg EE-containing COC.³⁸ Plasma levels of various substances were measured prior to, during, and after treatment. Unlike the 30 µg preparation, the 20 µg EE COC had no effect on plasma levels of factors VII and X.³⁸ Interestingly, significantly higher levels of factor VII were found in women treated with 30 µg EE/desogestrel-containing pills compared to a 30 µg EE/gestodene combination, supporting that the progestogen constituent may have a modifying effect.³⁸ In all treatment groups, fibrinogen, plasminogen

activity, and FDPs (particularly D-dimer) were found to significantly increase.³⁸ Conversely, PAI-1 antigen decreased in all treatment groups, while antithrombin III and protein C activity were unaffected.³⁸ Post-treatment, all variables reverted to their pre-treatment concentrations. Clearly, with an increase in coagulation activity, and a lack of change in the most important counter-measures to coagulation (ATIII and protein C), thrombogenic potential is enhanced by third-generation preparations. At a population level, this is exemplified by the doubling of DVT risk in third-generation users over second-generation users.³⁸ In a similar study comparing 20 µg EE to 30 µg EE preparations in 1633 women, results were somewhat consistent with previous findings.²⁸ In both treatment groups, F 1 + 2, D-dimer, and protein C activity were all shown to increase.²⁸ A decrease was observed in the activity of both antithrombin III and protein S.²⁸ Similar changes occurred in both treatment groups, but to a lesser degree in women receiving the 20 µg OC. Whereas in the study previously discussed, antithrombin III levels remained constant in the face of active coagulation, in this study, antithrombin III levels decreased despite the presence of active coagulation markers, and thus greatly exacerbated the potential for thrombogenesis. It can also be said that in this study, protein C levels increased, which may have provided sufficient anticoagulatory effects to avoid thrombogenesis.²⁸

At a molecular level, estrogens and progestogens, like other steroids, bind to their respective nuclear receptors in target cells. In the inactive state, estrogen receptors are sequestered in a complex comprised of the receptor itself, HSP-90, HSP-70, P59, and other proteins.^{39,40} Upon ligand binding, the receptor often dimerizes and associates with the steroid-dependent gene at an upstream response element (RE). Estrogen and progesterone have also been shown to participate in regulation of transcription through modification of transcription factor synthesis.⁴¹ In relation to hemostatic variables, factor XII is the only one whose gene contains a functional estrogen response element (ERE).²⁰ Gene transcription of factor XII is enhanced 6-fold in ovariectomized rats treated with 17- β -estradiol over untreated controls.⁴² Further evidence in the form of gel mobility shift assays, demonstrates a specific receptor/ERE interaction in the factor XII promoter sequence.⁴² Although tissue factor (TF) mRNA synthesis is enhanced by 17- β -estradiol in rat uterine epithelium, a functional ERE in the TF promoter has yet to be confirmed.⁴³ Von Willebrand factor (vWF) is another participant in coagulation whose synthesis is induced by 17- β -estradiol in human endothelial cells.^{37,44} Additionally, t-PA mRNA levels in human endometrial cells are enhanced by treatment with either estrogen or progesterone.^{45,46} Estrogen responsiveness seems to be localized to a site 7.1-Kb upstream from the transcriptional start site of the t-PA gene, whereas progesterone exerts its effects at a more proximal site.⁴⁷ Unfortunately, these same promoter fragments have not been isolated in endothelial cells, which are believed to be the source of plasma t-PA.^{48,50} A similar trend is observed with PAI synthesis: although PAI induction by estrogen and progesterone occurs in human endometrial cells, induction has yet to be observed in endothelial cell lines.³⁷

In summation, the 5' region of DNA in genes of t-PA, u-PA, PAI-1, and α -2-antiplasmin, have all been shown to contain at least a partial consensus EREs or PREs.²⁰ Highly variable with respect to target tissue expression, it is difficult to specifically link changes in hemostatic variables (other than in factor XII) to gene regulation by estrogen or progesterone. Despite subtle variation in the degree to which coagulation and fibrinolysis are activated by various COC preparations, there appears to be a balance in counterforces.

However, the balance that is achieved during OC use is unlikely to be regulated, and shifts in favour of coagulation or fibrinolysis may therefore occur.^{7,20}

Risk Factors for Thrombogenesis

The presence of additional risk factors in some women is paramount to the correlation between OC use and vascular disturbance. It is for this reason that a small subset of users manifest disease, while others appear to remain healthy. Risk factors for the development of venous disturbance (DVT, PVT, PE) are numerous. Those most commonly associated with VTE are obesity (BMI >30), immobility, excessive varicosities, and family history of DVT.^{4,5} In the obese individual, both fibrinogen and fibrin levels have been found to increase during OC use to a greater extent than in users with a BMI <25.⁵¹ Exercise has been shown to stimulate the fibrinolytic system,⁸ so in the chronically immobile person, it is easy to see how a diminished fibrinolytic response can lead to increased risk of thrombogenesis. Family history of VTE has been negatively correlated to antithrombin III levels.⁵¹ So, if a family history exists, an individual is subject to a decreased propensity to employ anticoagulatory measures. In addition, hypertension during pregnancy and rheumatic heart disease have been correlated to venous disturbance.¹⁶ Interestingly, the risk of vascular disturbance has not been correlated to parity, socioeconomic status, prior OC use or duration of OC use.¹³

More recently, increased risk of VTE has been attributed to receptor polymorphism and the factor V Leiden mutation. Polymorphisms of estrogen and progesterone effector pathways are believed to confer either hypo- or hyper-responsiveness to steroids in certain genes.²⁰ For instance, the factor VII gene is believed to respond with lesser magnitude to estrogen in the presence of MspI polymorphism.²⁰ This particular polymorphism destroys a cleavage site in factor VII, rendering the molecule less active in terms of coagulation.⁷² Those who possess the polymorphism (Arg to Gln substitution at position 353) are not factor VII deficient, but have a lower level of factor VII coagulant activity (factor VIIc), and a blunted response to estrogen. Those with the Arg/Arg genotype have considerably higher factor VIIc levels than do individuals with either an Arg/Gln or Gln/Gln genotype.⁷³ Additionally, women carrying the protective Gln allele showed no elevation of factor VIIc with use of HRT, compared to women with the Arg allele whose increase in factor VIIc levels coincided estrogen therapy.⁷³

The factor V Leiden mutation is simply a G/A substitution at nucleotide position 1691.⁵² In the presence of the mutation, the factor V APC cleavage site becomes inaccessible to APC, and thus thrombogenic potential is elevated. Factor V Leiden (FVL) occurs in approximately 20% of patients suffering idiopathic venous thromboembolism.⁵² In the general population, FVL is believed to be carried at a rate of 3-5%.^{52,53} FVL appears to be more prevalent than other genetic disorders of the anticoagulatory pathway such as protein C, S, and antithrombin III deficiencies.⁵² The risk of VTE in FVL positive individuals is quite high, and it is further compounded in those who are also using OCs. Compared to normal, non-user controls, the risk of developing VTE in a FVL individual (heterozygous) is 9 times greater.^{4,53} In OC users who are FVL+, there is a 30-fold increase in risk,⁵² while in third-generation users, the risk is 50 times greater than in normal controls.⁵⁴ Recalling that the risk of VTE in OC users is 3-4 times higher than in non-users, the FVL statistics intimate a synergistic relationship among risk factors. In other words, there are a significant number of women who will

develop VTE in the presence of both risk factors, who would remain healthy in the presence of only one. As such, the risk of VTE in a FVL+ OC user is the product of the individual risks associated with FVL and OC use.⁵² In the homozygous non-user, risk of VTE is elevated 100-fold.³¹ Fortunately, the frequency of homozygosity in the general population is only 1 in 5000.⁵²

Interestingly, carrier frequency varies according to ethnicity. In a study of 2468 Caucasian Americans, 5.27% were found to carry the Leiden mutation.⁵⁵ Out of 407 Hispanic Americans, 650 African Americans, and 442 Asian Americans, the carrier frequencies were 2.21%, 1.23%, and 0.45% respectively.⁵⁵ Finally, a study of 80 Native Americans revealed a FVL prevalence rate of 1.25%.⁵⁵ In light of this information, a possible explanation for why VTE is seen less often in the developing world may be related to low FVL carrier status, in addition to a distribution bias for third-generation pills.

Other inherited coagulopathies which predispose to thrombosis include antithrombin (AT) deficiency and Prothrombin 20210. Heterozygosity for AT deficiency, which has an autosomal dominant inheritance pattern, is associated with a significant lifetime risk of thrombosis,⁵⁶⁻⁵⁸ and has a population prevalence of 0.3%.⁵⁶ As AT deficiency can also be acquired (as seen with OC use, nephrotic syndrome, and pregnancy), women with the genetic defect may greatly elevate their risk of thrombosis by taking OCs. The prothrombin mutation 20210, also inherited in a pattern of autosomal dominance, arises due to a G/A substitution at nucleotide position 20210 of the PT gene.⁵⁶ This defect manifests itself as an increase in prothrombin levels. Prothrombin 20210 establishes a much weaker thrombotic risk than FVL, and is slightly less prevalent, with only 2-3% of the population heterozygous for the mutation.^{56,57,59} Not surprisingly, coinheritance of PT 20210 and the Leiden mutation compounds the risk of VTE.⁵⁹⁻⁶¹ Although elevation of coagulation factor concentration is, in itself, insufficient to confer hypercoagulability, recent evidence suggests that this may not be the case when referring specifically to factor VIII. Increased levels of factor VIII beyond 150% of normal has been shown to increase the risk of thrombosis by 4.8 times the risk of normal controls,⁶² suggesting that factor VIII level may indeed be an independent risk factor for VTE.⁵⁶ With 6-8% of the general population positive for high levels,⁶² factor VIII warrants consideration when screening for DVT/VTE risk factors.

The most frequently cited risk factors for arterial disease (such as CVA/MI) include smoking, diabetes, hypertension, age, obesity, and family history of MI or CVA.^{4,5,63} Although smoking is not correlated to venous disturbance,^{4,26,63} it has been shown to act synergistically with OCs to increase the risk of MI.^{8,64} Mechanistically, inhalation of nicotine is believed to induce a decrease in vascular prostacyclin production,⁸ thereby eliminating one method by which platelet aggregation and subsequent thrombus formation are inhibited. Indeed, nicotine use has been linked to a reduction of urinary prostacyclin metabolites in OC users,⁶⁴ thus favouring platelet aggregation.

In their 1994 study of hemostatic profiles in smoking and non-smoking women, Fruzzetti *et al.*, found increased levels of fibrinogen in both smoking and non-smoking pill users, suggesting that coagulation is favoured by OC use alone.⁶⁵ However, antithrombin III activity was shown to increase only in the non-smoking pill users, illustrating that a counterbalance to increased fibrinogen was lacking in OC-using smokers.⁶⁵ Furthermore, levels of tissue plasminogen

are elevated beyond normal in non smoking pill users, but not in smokers.⁶⁵ These data support the notion that fibrinolytic stimulation and subsequent neutralization of any OC-induced coagulation is a benefit derived in non-smokers only.⁶⁶ That the hemostatic balance is tipped to favour coagulation in smoking OC users is clear. Although this presents yet another compelling reason why young women should not smoke, it must be mentioned that the hemostatic effects cited occurred in women whose pills contained 35 µg EE. Recent evidence suggests that negative hemostatic profiles can be ameliorated by prescribing very low dose pills (ie, those containing 20 µg EE)⁶⁶ to both smokers and non-smokers. If these relatively new OCs become popular, a decreasing trend in OC-related thrombotic events may well be observed over the next decade, as the diminished risk associated with low EE may overcome the added risk of the third generation progestins desogestrel and gestodene.

Age is another interesting risk factor for stroke and MI. With advancing age, hemostatic changes occur, most notably in the form of decreased prostacyclin formation, decreased fibrinolysis, and increased platelet aggregability.⁶⁷ Today, OC use is proscribed in women over 40 because of this age-associated risk of MI.⁶⁸ In fact, many physicians will not prescribe OCs to healthy women over 35 years of age.⁶⁸ Age as a contraindication to OC use is becoming increasingly questioned with respect to its validity. Prior to 1976, women were not actively screened for risk factors such as diabetes, hypertension, and smoking. Naturally, the data collected from this time period (on which current OC practice is based) would have been confounded by the presence of these additional variables. Reanalysis of older data indicates that after controlling for other risk factors, the incidence of fatal MI in older OC users was the same as in non-users.⁶⁸ Not only are potential OC users screened for other risk factors today, modern pills rarely contain more than 35 µg EE, thereby diminishing the dose-dependent estrogen-associated risk of vascular disturbance.

Conclusions

In summation, women who manifest the risk of OC-induced thrombogenesis, are likely to have at least one other risk factor of cardiovascular disease, which will effectively push the precarious hemostatic balance towards coagulation. Although from a public health standpoint the burden of OC-associated disease is small, at an individual level, the consequences can be devastating. Approximately 50% of patients with PVT and 30% with DVT will suffer from post-thrombotic syndrome.⁴ This syndrome is a chronic complication characterized by symptoms of pain, swelling, and ulceration of the skin on the affected limb.⁴ Additionally, vessel reflux and obstruction are commonplace in those afflicted with the syndrome.⁴ There are several questions surrounding the issue of OC-related thrombogenesis that still remain unanswered. Cessation of OC use after the first thrombogenic incident is currently subject to much deliberation. While VTE carries a case fatality rate of 1-2%, the risk of maternal mortality in the developing world is far more significant. Approximately 1-8 women per 100,000 die annually because of OC-induced VTE, as compared to the 1800 maternal deaths per 100,000 live births that occur annually in Sierra Leone, for instance.⁶⁹ In fact, for all of sub-Saharan Africa, the average number of maternal deaths per 100,000 live births is 980.⁶⁹ Even the case fatality rate amongst OC users for MI (2.8 per 100,000) still does not compare to the risk of death incurred by pregnancy in developing countries. In North America, the risk of death from pregnancy exceeds that from cardiovascular disease attributable to OC use in all pre-

menopausal women.⁷⁰ This is true even though CV-related mortality is 10 times higher in pill users of the 40-44 age group than in those aged 20-24.⁷⁰

An issue of particular importance in North America, and of growing concern in the third world, is the added risk of thrombosis that OC users incur by smoking. It is no secret that while the prevalence of smoking has decreased in the general population, rates of tobacco use have been rising in certain age groups.¹² As a group, young women of the 15-19 age range are far more likely to smoke now than they were 10 years ago.¹² In chronological years, this age group directly precedes that in which oral contraceptive use is highest (recall that 38% of women aged 20-24 use the pill). In light of this trend, it may be prudent to prescribe very low dose pills (20 µg EE) to young women who smoke.

Another matter of concern is whether or not to screen for FVL and other such hereditary anticoagulation disorders. Arguments against doing so cite a lack of cost-effectiveness in screening, despite an exorbitant VTE risk posed for homozygous individuals.^{52,71} Furthermore, if FVL became a contraindication to OC use, approximately 4% of young women would be denied access to one of the most effective methods of birth control available today. On the other hand, screening for genetic mutations would undoubtedly save lives, if only a handful, and would allow the physician to counsel mothers and sisters of the carriers about their probable risk as well.^{52,71} Another advantage to screening for these disorders is that the patient could undergo prophylactic treatment during periods of high VTE risk, such as during post-operative immobilization. Ultimately, as our breadth of knowledge surrounding COC-induced vascular events becomes increasingly widened, the measures we implement to diminish the risk imposed on women, while at the same time providing fair access to OCs, must also reflect this growth.

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Robot-Assisted Surgery : A Review

Anand Govindarajan, B.Sc. (OT3)

Abstract

Robot-assisted surgery is the latest technology to be introduced into the operating theatre. It offers several advantages over conventional surgery, including greater spatial accuracy, increased dexterity and precision, reliability and reproducibility, measurable cost savings and ultimately better patient outcomes. However, its introduction into the surgical suite has been slowed by some of its drawbacks, such as large initial cost outlay, diminished operative field-of-view, decreased tactile feedback, and reduced flexibility to respond to major complications. As technology improves, it is likely that many of the disadvantages will be remedied and robots will play a greater role in future surgeries, as well as in other areas, such as telesurgery and surgical education. However, before robotics can be adopted by all surgeons, its economic and patient benefits must be demonstrated by more extensive clinical trials.

As technology becomes increasingly complex and powerful, it becomes a greater part of everyday life; medicine is just one of the areas that is being revolutionized by this technological invasion. From the urine-analyzing toilet in development in Japan to the complex tools used in the human genome project, technology assists all facets of medicine from diagnosing patients to elucidating the constituents of the human genetic code. One area that has caught great media interest in recent years is the use of robots in surgery. This article will briefly outline the history of the field, discuss the basic concepts of robot-assisted surgery, and explore some of the advantages, disadvantages, and future directions of this advancing area.

History

The success of pre-programmed and remote-controlled industrial robots in the 20th century, in terms of precision, cost-savings and superior performance, spurred the development of medical robots as a tool to enhance a physician's abilities. These developments led to their entrance into various fields including rehabilitation, laboratory automation and surgery.¹ Surgical robotics was first introduced in the 1980s into neurosurgery and orthopaedic surgery, due to the ability of the respective organ systems involved to provide fixed landmarks and the precision required in their respective procedures – manipulation of brain tissue in the former and precise cutting and joining of bone in the latter. Promising results in these fields subsequently led to the introduction of robotics into many other specialties including urology, otolaryngology, laparoscopic surgery and cardiac surgery. Telesurgery, an extension of robotic surgery involving the surgeon being physically separated from the operating robot,

was first considered by the U.S. military as a way of performing battlefield operations from behind battle lines.² In 1992, it was introduced as a concept in civilian medicine.³ Since then, several such robotic prototypes have been built that involve the surgeon operating the robot from a few metres away using a computer console and issuing commands by voice, joysticks and mock instruments. Clearly, surgical robotics have evolved a great deal in the last 20 years; to fully appreciate their impact on surgery, it is first necessary to consider some of the basic principles.

Basics

In order to understand surgical robotics, it is necessary to understand the most basic aspect of robotics – what is a robot? The Robot Institute at Carnegie Mellon University defines a robot as “a reprogrammable multifunctional manipulator designed to move materials, parts, tools, or specialized devices through various programmed motions for the performance of a variety of tasks.”⁴ Surgical robots are better termed “robotic devices” that share some of the features of the classical robot – they are highly variable in appearance, size, and function, as well as method of operation. Some are handheld while others are fixed to a support. Some perform a pre-determined operation upon command, while others respond by mimicking and enhancing a surgeon's hand movements – movements that are made on mock instruments or joysticks several feet away.

Surgical robots can be divided into two broad classifications – active and passive. The surgeon provides the physical force required to operate a passive robot, while an active robot does not require human power and is often computer-controlled.⁴ This affords active robots a degree of autonomy in performing their tasks that makes many of them intrinsically unsafe – that is, they have the capacity to execute unsafe motions. The earliest robots were both passive and intrinsically safe, but more advanced systems are active and not intrinsically safe; it is important to note that many robots can switch from active to passive mode over the course of the surgery.

Robots are currently used in many areas such as neurosurgery, orthopaedic surgery, urology, otolaryngology, and in endoscopic procedures such as lung resections and coronary artery bypass grafts (CABG).^{4,7} Some of these operations involve preoperative imaging with CT or MRI, and subsequent three-dimensional reconstruction to give an accurate view of the organ of interest. Certain operations (e.g., prostatectomy) utilize intrinsically safe robots, while others (e.g., stapledotomy) do not. Prostatectomies have been performed

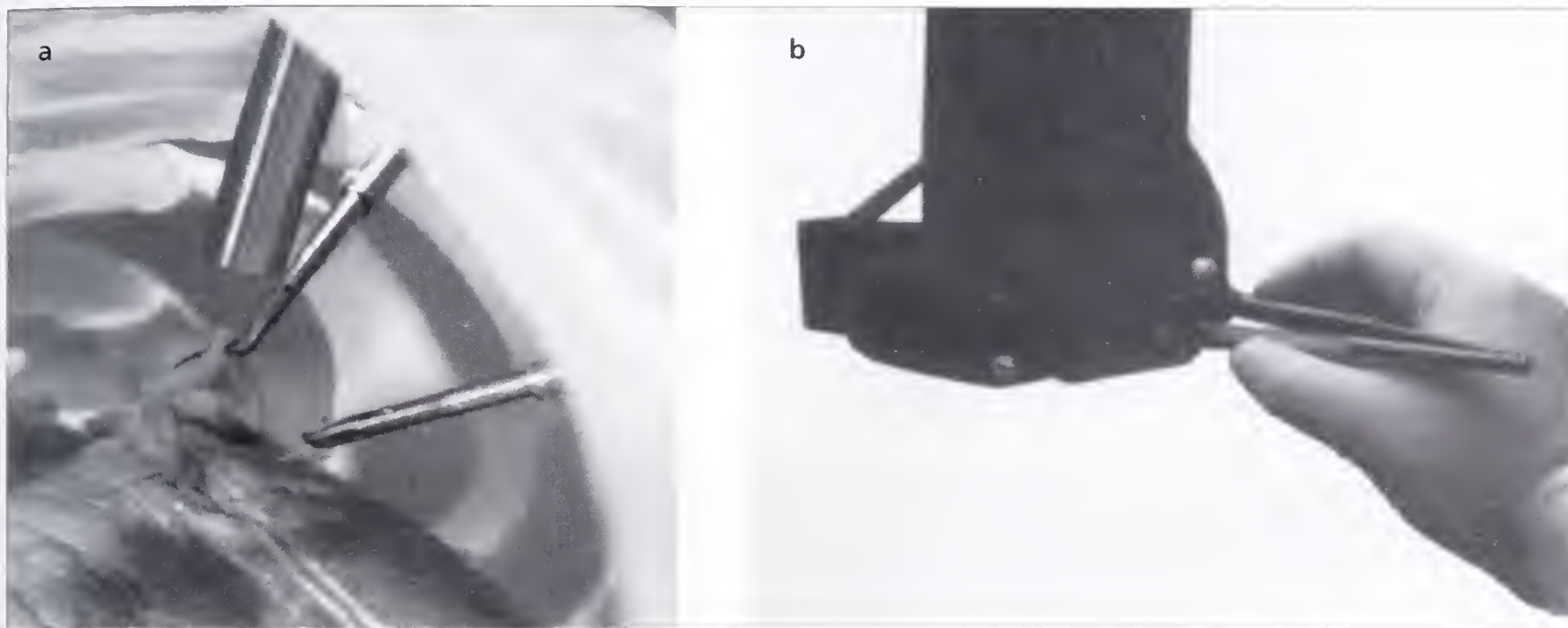


Figure 1. (a) The Zeus™ robot (Computer Motion Corp.) performing a CABG on a heart *ex vivo*. Performing on a live patient would be similar. (b) The surgeon's actions on the mock forceps attached to the computer console are translated to a similar instrument in the operating field.

transurethrally by a robot developed at Imperial College in London, which first images the prostate by ultrasound. The ultrasound tool is then replaced *in situ* by a cutting tool to ensure that the cutting field and the imaged field are identical.⁷ This restriction on the robot's movement makes this active robot an intrinsically safe one. Performing a stapedotomy involves removing most of the stapes and drilling a hole through its footplate. However, drilling through the footplate runs the risk of puncturing the oval window on which the footplate rests. The robot that performs this procedure tracks the cutting force and the work applied by the motor to determine when drilling should stop. Since the thickness of the stapes is variable, the amount of drilling that the robot performs cannot be preset. Consequently, the robot needs to make its own decision as to when to stop; an error can lead to a ruptured oval window and severe inner ear damage. Therefore, this active robot is not intrinsically safe.⁴

Advantages and Disadvantages

Robot-assisted surgery has many advantages over conventional surgery: greater spatial accuracy, dexterity and precision, reliability and reproducibility, and ultimately better patient outcomes.

By their very nature, computers have better three-dimensional spatial acuity than do humans. They are able to synthesize slices from a CT or MRI scanner into a three-dimensional organ, and are more precisely able to determine their own location relative to the organ. This has tremendous benefit in all areas of surgery, particularly neurosurgery. Currently, by coordinating a surgical robot with an MRI scanner, a surgical tool can be placed to within 0.5 mm of a lesion in the brain, compared to an accuracy of 1 mm when not coupled with the imager.³ The greater accuracy generated by MRI-guidance can lead to a more precise repair of the lesion. In addition, the robot can also plan the best route to follow to position the tool in the required location, thus minimizing collateral damage and resulting morbidity.³

Several factors contribute to the greater precision obtained when using a robot. It can be used to filter out a surgeon's hand tremor, enhance a surgeon's motions and perform accurate microscale movements that are otherwise impossible for a human to perform.

In addition, with the advent of voice-recognition technology, the surgeon no longer needs a human assistant to control an endoscopic camera, such as during a thoracoscopic lung resection or a laparoscopic cholecystectomy. Studies have shown that a camera controlled by the surgeon's voice instead of an assistant responding to the surgeon has the advantage of requiring significantly less field-of-view corrections and camera cleanings.^{5,8} As issuing commands to move the camera is a distraction to the surgeon, the advantages of using a robot-controlled camera whose movements require less correction are obvious. However, the disadvantages of this option include a longer setup time in one study⁸ and the inability of the robot to anticipate the surgeon's next move – something an experienced human assistant would be able to do.⁹

Reliability and reproducibility are also advantages inherent to the fact that robots are automatons. Given an algorithm, they will perform that algorithm precisely every time they are used. As a result, their behaviour is predictable and their actions are reproducible. It is of note that even the more advanced robots that are not intrinsically safe perform their actions in a predetermined manner and will perform a task identically on a given object every time. Clearly, such a degree of reproducibility is not achievable by humans.

Lastly, and perhaps most importantly, the use of robots can improve patient outcomes. Greater precision in operating on tissues such as the brain causes less damage to uninvolved tissues and thus reduced morbidity.³ In addition, robots allow endoscopic techniques to be used in areas previously thought to be inaccessible. Surgeons at the London Health Sciences Center at the University of Western Ontario recently performed the first closed-chest, beating-heart CABG in the world⁶ using the Zeus™ system; Figure 1 shows how such a revascularization is achieved in an *ex vivo* setting with the heart in a model rib cage. The surgery was performed with small pencil-sized incisions through which a camera and instruments were inserted into the patient's thorax. In addition to bypassing one vessel, some of the surgeries performed involved a second surgeon simultaneously revascularizing another vessel using angioplasty. Figure 2 shows several aspects of the da Vinci™ robot, another system that has been used to perform endoscopic cardiac surgery in several centres. Such procedures have several advantages for the patient. The endoscopic

...of the operation causes the patient significantly less pain, reduces the risk of bacterial infection, reduces the need for blood transfusions, and reduces the recovery time from over 7 days to 2 days.³ In addition, the ability to perform a second operation simultaneously means that the patient faces less operating time.

Despite all the advantages of robot-assisted surgery, there are some significant disadvantages, such as a limited field of view, reduced tactile feedback, and a diminished ability to respond to major complications.

First, in endoscopic surgeries, the surgeon has no "peripheral

vision", as he or she is restricted to the view provided by the robot-operated camera, and thus cannot have a sense of the situation immediately outside the camera's field of view, unless the camera is moved. In addition, the camera limits the surgeon to a two-dimensional view of a three-dimensional operating field. Although this problem has not been solved, some advances have been made to improve the situation. In neurosurgery, a neuronavigating wand has been developed that provides a three-dimensional view of the brain from the point of view of the wand.⁴ The image is synthesized from previously captured tomographic images of the brain. However, this method itself has disadvantages, including the altered appearance of

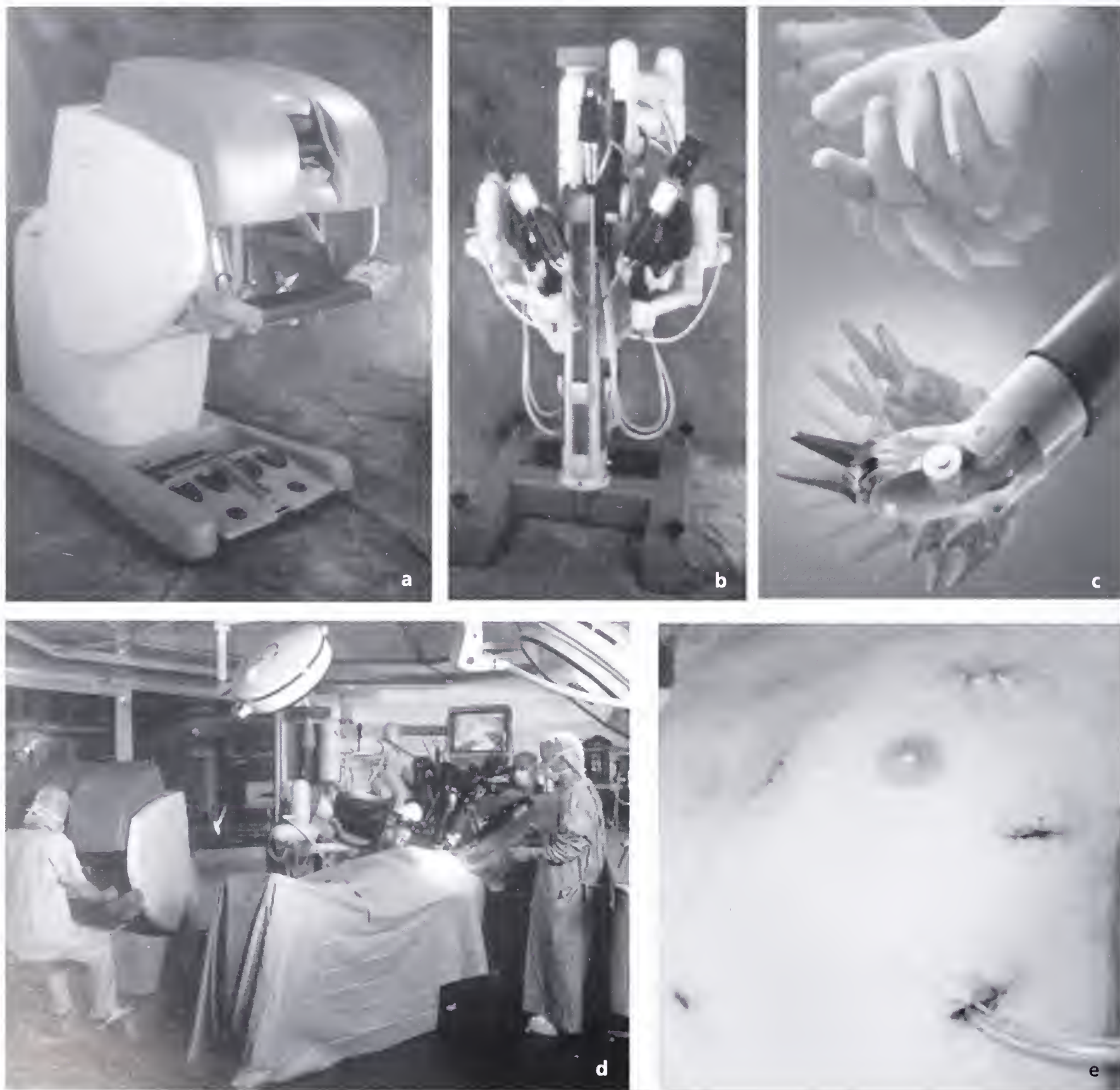


Figure 2. The da Vinci™ robot (Intuitive Surgical, Inc.) is one example of the type of robot used to perform complicated endoscopic surgery, such as cardiac surgery. Although this exciting system was developed in London, Ontario, it has been used elsewhere. (a) The surgical console used to control the robot from a distance. It contains foot pedals and transmits the surgeon's motions to miniature instruments. (b) The robotic arms. (c) The EndoWrist™ attempts to provide all degrees of freedom capable at the wrist. (d) A typical operating room setup with a robotic setup. (e) The chest of a patient who has undergone beating-heart endoscopic CABG. In comparison, the classical approach involving a sternotomy would result in a much larger midline scar with greater potential for infection.

the brain on imaging a closed skull compared with the craniotomized skull. In addition, attempts have been made to give the surgeon a better three-dimensional picture using stereoscopic techniques (left and right eyes seeing slightly different images) and shadow optics (using two different light sources, and three-dimensional interpretation of the resulting shadows); these methods, however, are currently only in the experimental stage.¹⁰

When piloting a robot that operates on a patient, surgeons are not provided with the same tactile feedback that they would have if they were operating on the patient directly. Although this is of little clinical relevance in simple operations such as cholecystectomies, it severely limits the ability to perform more complicated procedures such as tumour excisions, as this often requires palpation of the tissue to determine the precise location and margins of the tumour.¹⁰ Prototypes designed to overcome this problem have focused on two principles: the feedback force of the tissue on the instrument, and the response of the tissue to vibration applied by the palpating instrument are measures that reflect the firmness and consistency of the tissue being palpated. However, this technology is still in its infancy; as it improves, the quality of the sensory feedback should also improve.

Lastly, as robots are automatons, their ability to respond to major surgical complications such as arterial bleeding is limited.⁸ Consequently, there would be a delay before the surgeon could respond sufficiently to rectify the problem. If the complication was serious enough, this could lead to increased morbidity. This obstacle, and the concern over robots that are not intrinsically safe have understandably slowed the introduction of robots into surgery.

Future Involvement of Robotics in Surgery

Robotic surgery is a rapidly advancing field that could be applied to several new areas. The ability to miniaturize technology has led to the field of microrobotics. Some current or potential uses of this technology include internal sensory devices, drug delivery systems, biopsy samplers, and artificial valves and sphincters. However, one of the most interesting areas where microrobotics is being explored is that of colonoscopy, where a microrobot could propel itself through the colon, documenting its journey along the way.¹¹ A prototype that has shown promising results in vitro uses vacuum suction to adhere to and “walk” on the colonic wall, relaying information back to the endoscopist as it proceeds.¹²

A second area that is actively being examined is surgery in remote locations, an extension of the current limits of telesurgery. Already, robotic surgery is performed in a setup in which the surgeon is located several metres away from the patient, issuing commands to the robot that is operating on the patient. It is natural to try to extend this to performing surgery in more distant locations. However, several issues make its implementation difficult: the reliability of transmission lines, latency in transmission, and the ability to respond to complications. The latency in transmission time over remote distances restricts remote surgery to be performed over several hundred kilometres, and prevents data from being transmitted via satellites.³ One preliminary study that examined the effect of time delays on robotic surgical tasks showed that surgical accuracy decreased and the number of operator errors increased as the time delay in robotic response time and visual acquisition increased; a surgeon could only adequately compensate for a delay of less than 700 msec.¹³ Although transmission delay is an important problem, the inability of a robot to respond to complications is possibly the most

important concern and is the most difficult to remedy, given the relative inflexibility of current surgical robots. As robotic technology advances, it is likely that robots will become more flexible in their movements and programming, and will be able to adaptively respond to complications as they arise.

Lastly, surgical education can be improved with the addition of robots to operating rooms. Currently, endoscopic surgery involves the surgeon looking at an image on a screen instead of at the real patient; it is thus plausible for the image to not be of an actual patient but of a virtual one, and for the surgeon to “operate” on this patient.³ In addition to a role in education, such simulated surgeries also have a role in preparing experienced surgeons for difficult and complicated operations.

Are Surgical Robots a Panacea?

As discussed earlier, robotic surgery can allow endoscopic surgery to be performed in new fields such as cardiac surgery, and this can lead to better patient outcomes, partly through faster recovery times. In these days of financial constraints, this is a desirable outcome as patients can leave the hospital earlier, resulting in substantial savings. It has been estimated that the cost savings could be as much as C\$1,400 per day for an intensive-care bed.⁶ In addition, the use of robot-controlled laparoscopic cameras can free full-time staff to perform other tasks, thus saving on manpower costs as well. However, these savings come at a steep price, as the technology required to perform robot-assisted surgeries can cost up to \$1 million (in the case of the ZeusTM and da VinciTM systems) – money that might be better spent improving other aspects of patient care. A reasonable compromise might be to invest in technology that is compatible with the instruments and facilities already present at a hospital;¹⁴ the Toronto Hospital currently has plans to build several new operating theatres into which robotic surgical systems will be incorporated.¹⁵ However, it is important to remember that the movement towards technology should not be driven primarily by economics, but by patient outcomes.

Although surgical robotics is rapidly advancing, it is still a relatively new field that is untested on a large scale. In July, 2000, the FDA approved the first telesurgical robot, which involves the surgeon operating a console a few metres from the patient; the clinical trials on this robot involved 113 patients.¹⁶ Inevitably, other robots will also be approved by the FDA, and hospitals will need to address the issue of whether surgical robots are the most effective use of funds in terms of patient morbidity and mortality. In the free-market environment of the U.S., the centres that first espouse robotics will undoubtedly use it as a marketing tool to attract patients to their clinics, as they did over 10 years ago when laser treatment for coronary blockages showed promise.² Just as it was later shown that this laser treatment was not beneficial, it is possible that robotic surgery may not benefit all patients. Well-designed, extensive trials are needed to determine who would benefit most from this technology, and whether the benefits of robotic surgery outweigh its costs.

Conclusion

Technology is becoming an increasing part of all facets of medicine, and surgery is no exception. Robotics is a rapidly expanding field that is revolutionizing the way surgery is performed. Its many potential advantages, including improved patient outcome, cost savings and educational utility make it an attractive area of development for those hospitals able to afford the large initial investment. However, cost savings and educational use are secondary con-

...considering robotic surgery – improved patient outcomes should be the primary goal that drives the expansion of its use. To this end, more trials are required before the use of robotic surgery is deemed beneficial to patients and can be accepted by surgeons.

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Review of Methods Used to Estimate Patient Benefit from Middle Ear Surgery to Correct Unilateral and Asymmetric Conductive Hearing Loss

Jon Kian Nia B.Sc. (OT3)

Manohar Bance MB, MSc. FRCS(C)*

Sharif Missiha B.Sc. (OT3)

Abstract

The goal of otologists performing middle ear surgery to correct unilateral conductive hearing loss is to improve hearing as well as to provide a functional benefit to the patient. Unilateral conductive hearing loss is associated with various disabilities including difficulty in sound localization and in hearing and understanding speech. Traditionally, otologists have reported the results of middle ear surgery as the closure of the air-bone gap or the reduction in air conduction thresholds. The closure of the air-bone gap refers to improvement of the air conduction thresholds (involving conductive and sensorineural components) to the level of the bone conduction thresholds (sensorineural component). While these provide a measure of the technical success of the operation, they may not always translate into real life benefit for the patient. This is because listening is a binaural task, while the benefit to the patient is determined by factors such as hearing in the non-operated ear. In this paper, the two most common methods used to estimate patient benefit from middle ear surgery are reviewed; these methods are the Glasgow Benefit Plot and the Belfast Rule of Thumb. Both methods are based on perceived subjective benefit to patients. In fact, little objective data currently exist that measure the benefit to patients undergoing middle ear surgery. In this discussion, a new, more objective method is introduced, with preliminary evidence that supports the validity of the standard current methods.

Introduction

Both ear surgeons and patients alike hope for an improvement in hearing and also a functional benefit from middle ear surgery to correct unilateral conductive hearing loss. The potential benefit for any surgical procedure is different depending on specific patient characteristics. In particular, unilateral or grossly asymmetric conductive hearing loss is challenging for ear surgeons. If hearing is much better in one ear, the benefits of improving the hearing in the worse ear are not as clearly defined as they are in bilateral symmetric hearing loss. In the latter case, there is an obvious increase in benefit with any improvement in hearing.

The principle objective of this paper is to review some of the disabilities associated with unilateral conductive loss, as well as two methods of predicting patient benefit from middle ear surgery, and preliminary data that validate the methods outlined.

Unilateral Hearing Loss

In adults, unilateral hearing loss is commonly associated with difficulty in sound localization, difficulty in hearing and understanding speech from the affected side, and difficulty understanding speech in the presence of background noise.^{1,2} Children with unilateral hearing loss also experience difficulties with word comprehension, attention, storytelling, responsibility, completion of assignments, and the ability to adapt to new situations.³ The subjective advantage of binaural listening includes increased ease of listening, increased volume and spatial balance, improved sound quality, and greater success listening in difficult listening situations.⁴⁻⁸ Unilateral hearing often results in a decrease in those aspects that are associated with binaural hearing.

Many patients who present to an ear surgeon with a conductive hearing loss have only one ear impaired. In addition, with bilateral conductive loss, the degree of hearing impairment is often asymmetric. Traditionally, the most common methods used to assess hearing improvements from middle ear surgery have been the post-operative closure of the air-bone gap and improvements in air conduction thresholds. The first method measures the technical success of the operation, while the second method measures the decrease in monaural disability. While this improvement in hearing is a desirable outcome, it does not always translate into real life benefit, since neither of these methods takes into account the role of the contralateral ear in hearing. Furthermore, as with any surgery, there are many technical risks associated with middle ear surgery, which must be balanced against potential benefits. In particular, the risk of damage to the inner ear must be considered.

Other methods have been used to evaluate the effectiveness of middle ear surgery including questionnaires that evaluate a patient's subjective benefit from surgery. Using questionnaires to evaluate benefit is complicated by the fact that both surgeons and patients want to believe that the operation has succeeded. At the present time only subjective interpretations are available, although more objective measures would be desirable. The two

*Consultant Otolaryngologist, Department of Otolaryngology, The University of Toronto; and Otolaryngologist, The Toronto General Hospital University Health Network

most common methods found in the otologic literature to evaluate patient benefit from middle ear surgery are the 15/30 dB 'Belfast Rule of Thumb'⁹ and the Glasgow Benefit Plot.¹⁰

Belfast Rule of Thumb

Smythe and Patterson developed the Belfast Rule of Thumb⁹ based on analysis of the relationship between the patient's perceived subjective benefit and post-operative audiometric changes. The subjective perception of operative success compared with the degree of symmetry indicated that the least satisfied patients were those whose degree of symmetry differed by more than 15 dB. (The degree of symmetry is the difference in hearing between the ears.) The results showed that patients were likely to report significant benefits if the average air conduction threshold (for 0.5, 1, 2 kHz) was ≤ 30 dB or the interaural difference ≤ 15 dB. The putative reason behind this theory is that because the skull does not greatly attenuate the transfer of sound energy, speech impinging on the poorer hearing ear will be heard mostly by the better ear, unless the difference in air conduction thresholds is 15 dB or less.¹¹ However, it can be safely assumed that any patient with bilateral hearing loss of ≥ 70 dB will benefit considerably from any surgery that reduces the air conduction thresholds to less than 40 dB in only one ear.

Glasgow Benefit Plot

The Glasgow Benefit plot¹⁰ (Figure 1) is a graphical method of reporting surgical results. This plot has the advantage of allowing one to visualize both the absolute air thresholds in each ear, and the asymmetry by plotting the pre-operative and post-operative results of the air conduction thresholds in both ears. Patients fall into one of three pre-operative impairment groups (1-3), shown in Figure 1; the post-operative results fall into one of four groups (a-d). Joining the pre-operative and post-operative data points produces a vertical line, with the length representing the improvement in air conduction; the benefit depends on the area of the graph in which the line ends (the final hearing result). Patients who fall into groups 'a' and 'b' are likely to achieve significant benefits, while those who fall into 'c' and 'd' are unlikely to achieve significant benefit. For

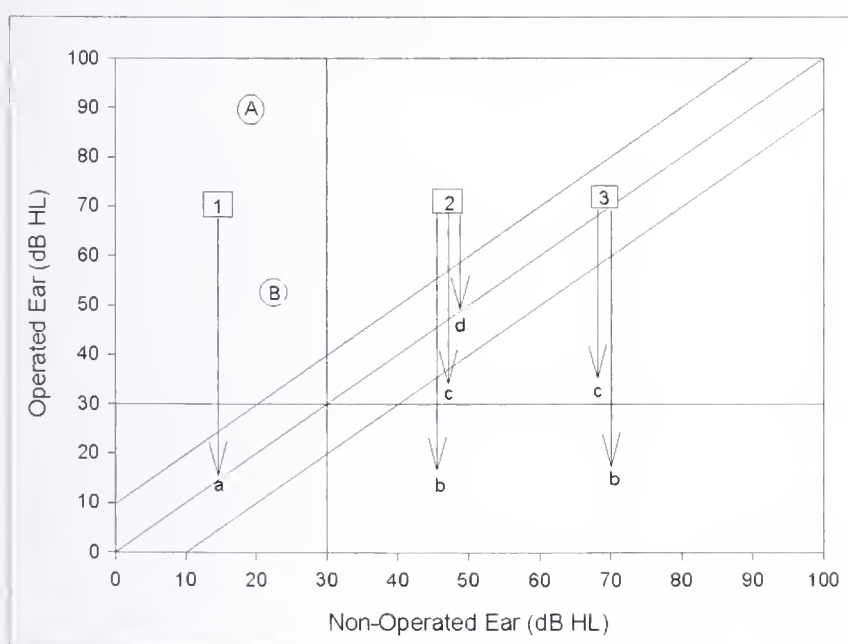


Figure 1. The Glasgow Benefit Plot. The pre-operative area is divided into three parts: (1) unilateral hearing loss, (2) bilateral asymmetric hearing loss, (3) bilateral symmetric hearing loss. The post-operative area is divided into four parts: (a) normal hearing, (b) normal unilateral hearing, (c) bilateral impaired hearing with better operated ear, (d) symmetrically impaired hearing. Refer to the text for explanation of 'A' and 'B'. (Adapted from reference 10).

example, a 50 dB improvement in a patient with air conduction thresholds at point A on the graph would not result in a change in the auditory status. In contrast, a smaller improvement of 30 dB in a patient at point B on the graph would change the auditory status and may reflect a significant benefit to the patient.

Discussion

The Belfast Rule of Thumb and the Glasgow Benefit Plot are similar in predicting benefit for patients presenting with unilateral or asymmetric conductive loss. For example, a patient with mixed hearing loss (HL), with an air conduction average of 80 dB HL, bone conduction average of 40 dB HL and a normal contralateral ear would not be indicated for surgery by these methods. This finding makes sense because even if the air-bone gap were to close, the impaired ear would not be significantly involved in the listening process because of the normal contralateral ear. However, a patient presenting with a perforated eardrum, with an air conduction average of 60 dB HL, normal bone conduction thresholds and a normal contralateral ear would be indicated for surgery. In between these two examples, there are many factors to consider such as the degree of asymmetry, the nature of the pathology, the use of hearing aids, inner ear reserve, and patient motivation, before performing middle ear surgery.

Speech-in-noise tests have also been used to assess the effects of unilateral conductive loss. Audiological tests using speech stimuli to assess hearing ability in patients is advantageous because speech is the most important and widely used auditory stimulus in everyday listening situations.

Using a speech-in-noise test, Feurstein found that simulated conductive unilateral hearing loss reduced ease of listening when background noise was present.¹² In addition, he found that word recognition in background noise was decreased significantly with a simulated unilateral conductive hearing loss. This effect was more pronounced when the speech originated from the side of the hearing loss.¹²

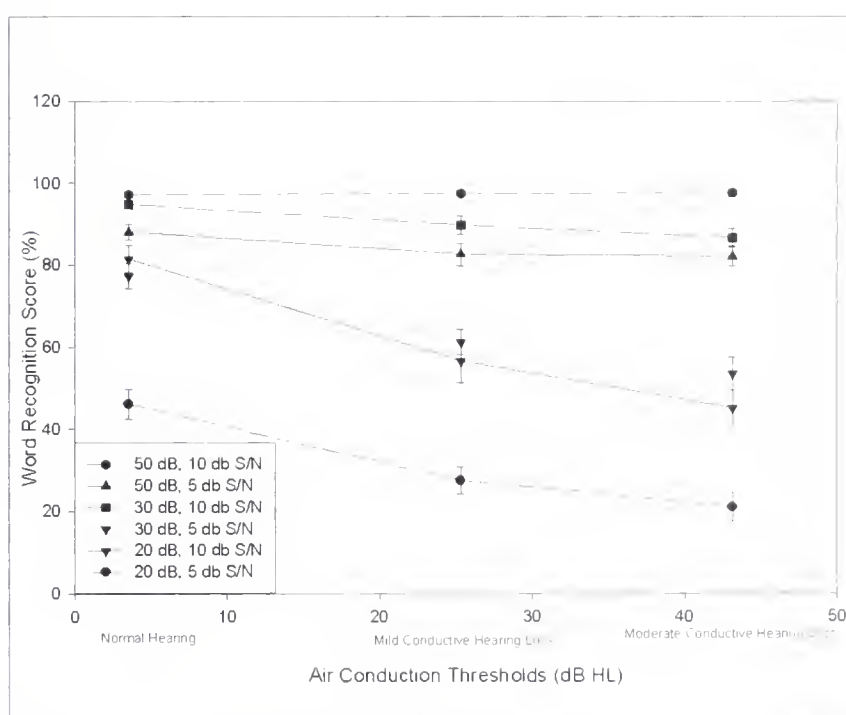


Figure 2. Word Recognition Score (%) versus Air Conduction Thresholds (dB HL) at 50, 30 and 20 dB HL, 10 dB and 5 dB S/N ratio for increasing unilateral conductive loss. The standard error is represented in the error bars.

Nia and Bance (unpublished data) used a speech-in-noise test to assess the effect of asymmetric conductive hearing loss on word recognition in background noise. Figure 2 shows the results of these experiments. Word recognition score on the Y-axis represents how well subjects recognized speech in background noise. The X-axis represents the air conduction thresholds, where higher thresholds represent increasing unilateral conductive hearing loss in the same set of subjects, simulated by two earplugs. The word recognition score is highest when the presentation level is 50 dB and the signal-to-noise (S/N) ratio is 10 dB, and decreases thereafter if either the presentation level or the S/N ratio is decreased. The word recognition score also decreases significantly with increasing unilateral conductive loss. These results reveal that there is a disability associated with unilateral conductive hearing loss in the presence of background noise. The effect is much more marked for low volume sounds (the word recognition score is lowest at the presentation level of 20 dB) and for sounds with competing background noise (the word recognition score is lower at 5 dB S/N ratios than at 10 dB S/N ratio at any particular presentation level). It appears that increasing presentation level can overcome this disability (note the improvement in word recognition score at 50 dB). Thus, the disability of a unilateral conductive loss depends on both the S/N ratio and the presentation level. In addition, the absolute value for the slope from 25 dB to 4 dB is 1.9 times higher than the slope from 43 dB to 25 dB. This means that the disability associated with monaural hearing does not increase in a linear fashion with increasing unilateral conductive loss.

These results are consistent with the Belfast Rule of Thumb and the Glasgow Benefit Plot. For simplification, one might assume that increased word recognition in background noise is equivalent to increased benefit to the patient. A preliminary study by Nia and Bance found that for every decibel decrease in unilateral conductive hearing loss, the benefits in speech recognition were 1.9 times higher when the unilateral conductive loss was decreased from 25 to 4 dB, than when it was decreased from 43 to 25 dB. Given this finding and our assumption, the same amount of improvement in the air conduction thresholds is likely to be of higher benefit to the patient at lower levels of asymmetry than at higher levels of asymmetry. For example, a 15 dB improvement in hearing for a patient with a small unilateral conductive loss (average air conduction thresholds of 25 dB) will result in 1.9-fold greater benefit than a 15 dB improvement in a patient whose average air conduction thresholds are at 43 dB. This analysis is supportive of the Belfast Rule of Thumb and the Glasgow Benefit Plot.

Currently, the Belfast Rule of Thumb and the Glasgow Benefit Plot are the most common methods used to estimate patient benefit from middle ear surgery to correct unilateral and asymmetric conductive hearing loss. In fact, other methods of estimating patient benefit were not found in an extensive literature search. Both of these methods stress the importance of the final hearing level in the better hearing ear, and the degree of asymmetry as the major determinants of patient benefit. Both of these studies were conducted using patients' subjective interpretations. The rules indicate that the patient has significant benefit only if surgery results in air conduction thresholds of ≤ 30 dB in the impaired ear or the level of hearing is within 15 dB of the contralateral ear. These methods of estimating

patient benefit are consistent with our understanding of sound energy attenuation through the skull from one ear to the other. Furthermore, a study by Toner and Smythe found that patients' estimate of benefit was significantly correlated with both the Belfast Rule of Thumb and the Glasgow Benefit Plot.¹³ The latest study using speech-in-noise testing also indicates that the improvement in word recognition score is less at higher levels of conductive loss or higher levels of asymmetry. These results further validate the Glasgow benefit plot and 15/30 rule of thumb in the population of patients used for that study. More research is required to more objectively quantify the potential benefit of middle ear surgery. However, at the current time, the Belfast Rule of Thumb and the Glasgow Benefit Plot seem to be the best methods for predicting patient benefit from middle ear surgery to correct unilateral and asymmetric conductive hearing loss.

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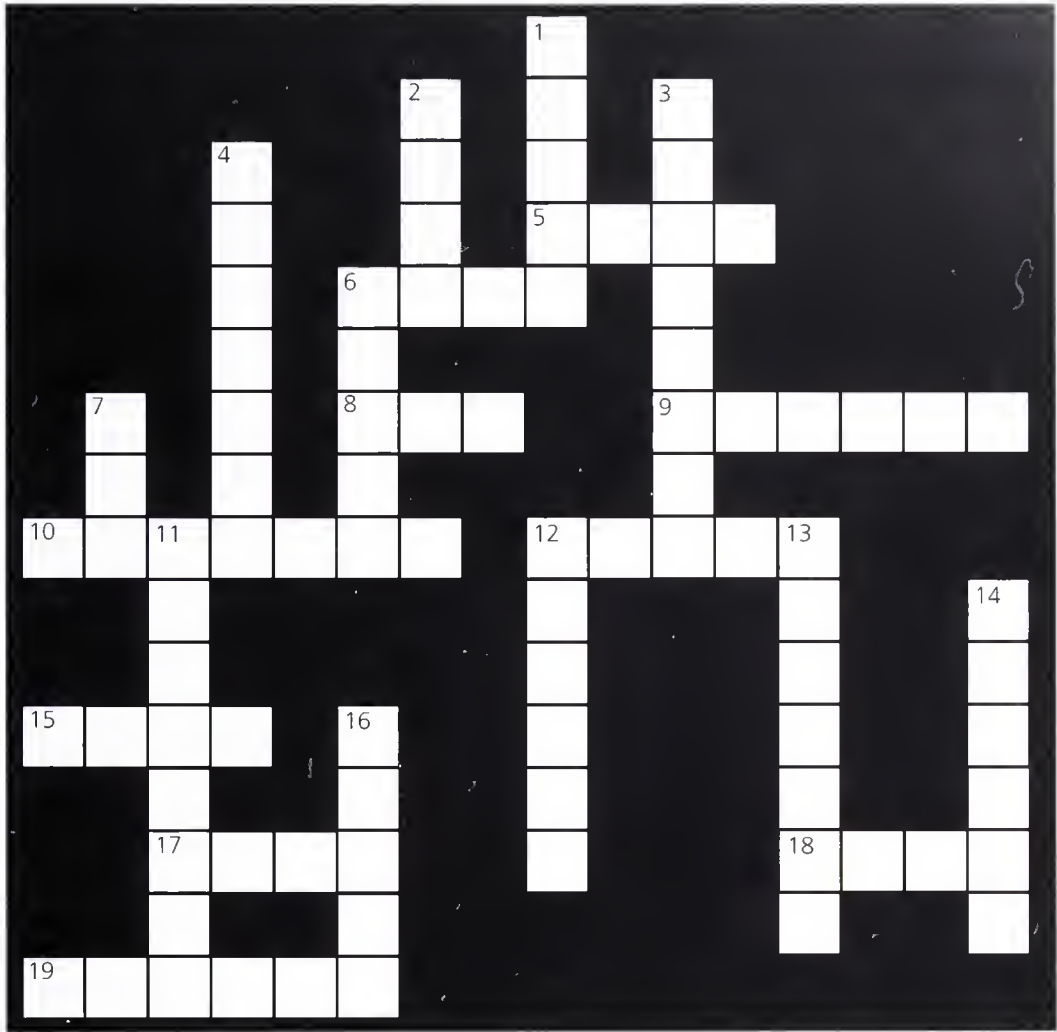
UTMJ Crossword (answers on page 144)

The *UTMJ* experience should not be confined to your desk or office- it is more than just an informative medical journal. Take your copy home and let *UTMJ* work for you!

AT HOME WITH YOUR UTMJ

Aside from highly informative bathroom reading, UTMJ can make your home a better place. Looking to redecorate? Look no further than your copy of UTMJ!

- 1. Impress friends and family with your coffee table I.Q.
- 2. Grace your bare walls with our lovely graphic designs
- 3. Three words: Coasters, Coasters, Coasters.
- 4. Think big, (we are not sure how to do it but...) think furniture: a couch, a dining room table, a handsome armoire, perhaps?
- 5. But remember to carefully preserve the UTMJ Crossword. Retire to a quiet corner and savour its intellectual, article-related sustenance most serene.



Across

- 5 Tator's research focus; syn. electrical cable (4)
- 6 ___ to Basics (4)
- 8 Two-headed medical marvel (3)
- 9 H. Shah claims this is within us (6)
- 10 Free music, not love (7)
- 12 UTMJ column; platform for discussion (5)
- 15 Latest med student play- thing; tropical tree (4)
- 17 Access to Medicine- ___ trade? (4)
- 18 ___ and Views (4)
- 19 Internal Med's "Big Book" (6)

Down

- 1 Lovely chocolate drink; ___ Diagnosis (5)
- 2 Shared name of Teletubbie and UTMJ editor (4)
- 3 Thursday Med Student preoccupation (8)
- 4 A Young Doctor can receive these (7)
- 6 P. Giacomini's Synonym for "Neurology in Clinical Practice" (5)
- 7 Watson's big passion (3)
- 11 Quality of profiled scientists (8)
- 12 Social support; UTMJ is your ___(6)
- 13 Med student's difficult time of day; ___ report (7)
- 14 Recently divorced Kidman; Crossword editors would like to be on a ___ (6)
- 16 Scenic landscape; News and ___ (5)

In the Literature

Philippe L. Bedard, B.ArtsSc. (OT3)

This section of News and Views will present updates of recent advances in the medical and scientific literature.

Progress Towards a Vaccine for Alzheimer's Disease

Alzheimer's Disease (AD) is associated with the formation of neurotoxic plaques due to the accumulation of amyloid- β (A β) peptide. However, it is unclear from past research whether the progressive dementia of AD is caused by the abnormal build-up of A β . Two papers published in the December 21/28 issue of *Nature* provide compelling evidence for a causative role of A β accumulation in AD. Janus *et al.* and Morgan *et al.* studied the functional effects of vaccination with A β in transgenic mice predisposed to develop AD. Earlier work demonstrated that when vaccinated with A β , mice predisposed to develop AD formed antibodies to A β and showed reduced neurotoxic plaque formation. To determine whether A β vaccination could protect against the cognitive dysfunction seen in AD, both groups used similar tests of spatial memory. In these tests, the mice had to swim to and mount a platform located invisibly beneath the surface of a pool of water. Janus *et al.* tested "spatial-reference" memory: the platform remained in the same location for every trial over each five-day testing period and the mice were tested longitudinally at four-week intervals to track changes in learning and memory over time. In contrast, Morgan *et al.* tested "episodic-like" memory: the platform remained in the same location for every trial in each day of testing, but was moved about randomly from day to day to test short-term memory. Both groups found that mice vaccinated with A β did not show the age-related decline in performance seen in non-immunized controls. Interestingly, both groups found that although vaccination with A β reduced the number and size of A β plaques, it did not completely eliminate plaque formation. In addition, Janus *et al.* reported no overall decrease in the amount of A β peptide. Both groups suggest that either a small or a selective reduction in A β levels may be sufficient to protect against AD dementia. In summary, these two papers suggest that A β plaque formation may be responsible for the cognitive dysfunction of AD and provide hope that a human vaccine against A β may be successful in preventing AD in the future.

Janus C, Pearson J, McLaurin J, *et al.* (2000). *Nature*. 408: 979-82.
Morgan D, Diamond DM, Gottschall PE, *et al.* (2000). *Nature*. 408: 982-85.

Hip Protector Reduces Incidence of Hip Fractures in Elderly

Hip fractures are a significant cause of morbidity and mortality in the elderly population. They are usually the result of a fall or other traumatic event producing direct impact to the greater trochanter of the femur superimposed on an underlying structural weakness in the bone caused by osteoporosis. Current methods of hip fracture prevention are aimed at either reducing the risk of falling or reducing the severity of osteoporosis. Kannus and colleagues investigated the use of hip protectors to prevent hip fractures in a large-scale trial in

Finland. The protector used was a padded shield covering the greater trochanter worn inside a pant pocket or on a stretchy undergarment. Their trial involved subjects 70 years old or older receiving care at any of 22 community health-care centres in Finland, who had one or more identifiable risk factors for hip fracture. These included a previous history of falls or fractures, impaired balance or mobility, or cognitive impairment. Randomization to either hip protector or control groups was performed in a 1:2 ratio according to health-care centre. At baseline assessment, there were 446 subjects in the hip protector group and 981 subjects in the control group. During the study, 13 subjects in the hip protector group had a hip fracture, as compared with 67 in the control group. Nine of the 13 fractures sustained in the hip protector group occurred while the subject was not wearing a hip protector. The authors concluded that among elderly adults who are at risk for hip fracture, the risk of fracture can be reduced by 60 percent by the use of a hip protector. Additionally, their calculations suggest that in order to prevent one hip fracture per year, only 41 elderly persons need to use the protector for a year. Although compliance with wearing a hip protector may limit the effectiveness of hip protectors as a fracture prevention device, these findings suggest a powerful method for reducing the risk of fractures and should be considered in all persons at increased risk.

Kannus, P, Parkkari, J, Niemi, S *et al.* (2000). *NEJM*. 343: 1506-1513.

Fetal Cell Therapy Improves Motor and Cognitive Function in Patients with Huntington's Disease

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disease characterized by a progressive loss of GABA-containing neurons in the striatum and cerebral cortex. Although some of the symptoms of HD, such as chorea, psychosis, and depression, can be alleviated by medication, there is currently no effective therapy for this disease in humans. However, in animal models of HD, intrastriatal grafts of fetal striatal neuroblasts were shown to form a striatum-like complex with functional neuronal projections to the cerebral cortex. These reconstituted structures were sufficient to cause a reversal of the motor and cognitive deficits seen in rats and monkeys with HD. In a preliminary report published in *The Lancet*, Bachoud-Lévi and colleagues describe five patients with symptomatic Huntington's disease who received two intrastriatal grafts of neuroblasts, separated by a one-year interval, from 7.5-9 week old human fetuses. Three of the five patients showed graft survival one year after the second graft implantation. Graft survival was demonstrated by increased or stable metabolic activity throughout the striatum on PET imaging when compared with pre-implantation data. Interestingly, the three patients with surviving grafts showed improvements in neuropsychological testing, activities of daily living,

and a reduction in the severity of chorea and bradykinesia. In contrast, the two other patients who showed decreased metabolic striatal activity following graft implantation demonstrated worsened cognitive and motor function 1 year post-implantation. Similarly, a cohort of 22 patients with HD who were assessed in parallel showed worsening chorea and neuropsychological performance. Although these findings are preliminary and have only been demonstrated in a small sample of HD patients, they suggest that there may be a role for fetal cell-replacement therapy in the treatment of HD in the future. A larger multi-centre study is currently in progress to determine the therapeutic benefit of fetal cell-therapy in HD.

Bachoud-Lévi A-C, Rémy P, Nguyen J-P, *et al.* (2000). *Lancet*. 356: 1975-1979.

Regular Source of Care Among Physicians

Studies of the general population indicate that individuals who use a single physician to manage primary health care needs, known as a regular source of care (RSOC), are more likely to use preventive health services and enjoy shorter lengths of stay when admitted to hospital. Past research also suggests that physicians' personal health habits and disease screening practices influence the preventive health counseling they provide to their patients. Gross and colleagues surveyed all of the physicians who graduated from the Johns Hopkins School of Medicine between 1948 and 1964 to investigate the use of an RSOC among physicians, and to determine whether having a RSOC was associated with the subsequent receipt of preventive health services. 915 physicians completed their survey (77% response rate) and 312 (35%) indicated that they did not have a RSOC. The use of a RSOC varied according to medical specialty, as pathologists, surgeons and internists were less likely to have a RSOC than pediatricians and psychiatrists. Respondents who did not have a RSOC were almost twice as likely to believe that chance or fate determines health outcomes and were less likely to believe that health professionals determine health. Not having a RSOC also predicted not being screened for breast, colon, and prostate cancer, as well as not receiving influenza vaccination. This study did not directly investigate whether having a RSOC influences the quality of care provided by physicians to their patients. The authors suggest that the use of a RSOC and preventive health services among physicians is sub-optimal, given that physicians are not only aware of the purpose and efficacy of preventive services, but also have greater access to these services than the general population. The authors recommend that physician organizations encourage physicians to have a RSOC and that medical education stress the importance of appropriate personal health care to medical students.

Gross CP, Mead LA, Ford DE, and Klag MJ. (2000). *Arch Intern Med*. 160: 3209-3214.

Cellular Telephone Use is Not Linked to Brain Cancer

There are currently an estimated 500 million cellular telephone users worldwide. Concerns have been raised about the possible adverse health effects associated with cell phone use, especially the possibility that low-power radiofrequency signals transmitted by the antennas might cause brain tumors. The evidence for such thinking is largely anecdotal, as there is no commonly agreed upon scientific mechanism by which a carcinogenic effect of low-power radiofrequency would be mediated, and there is little epidemiological research on exposure to low-power radiofrequency. Two retrospective case-control studies published in the *Journal of the American Medical Association* and the *New England Journal of Medicine* found no association between handheld cellular telephone use and the risk of brain cancer. Muscat and colleagues surveyed 469 primary brain cancer patients and 422 age-matched controls at five US medical centers between 1994 and 1998 and found no statistically significant

differences in the number of years of use, hours per month, or total cumulative hours of cellular phone use between brain cancer patients and controls. Additionally, within the brain cancer patient group, there were no associations between cell phone use and the site or histologic subtype of tumour or cellular phone handedness and tumor laterality. Similarly, Inskip and colleagues conducted interviews with 782 primary brain cancer patients and 799 age-matched controls at four US medical centers between 1994 and 1998 and found no evidence of increased brain cancer risk among persons who used cellular telephones for 60 or more minutes per day or regularly for five or more years. They also did not find any association between cellular phone use and histologic tumour subtype, or cellular phone handedness and tumor laterality. Although these studies are limited by both recall bias and the recent changes in cellular telephone technology as well as their ability to detect whether cellular telephones might increase cancer risk following a long latency period, they suggest that short-term exposure to low-power radiofrequency signals emitted by cellular phones does not cause brain cancer.

Muscat JE, Malkin MG, Thompson S, *et al.* (2000). *JAMA*. 284:3001-07.

Inskip PD, Tarone RE, Hatch ME, *et al.* (2001). *NEJM*. 344:79-86.

A New Link Between Pesticides and Parkinson's Disease

Although the cause of idiopathic Parkinson's disease (PD) is unknown, epidemiological studies suggest an association with exposure to pesticides and other environmental toxins. The theory of toxin-mediated damage leading to PD was fueled by the appearance of an outbreak of parkinsonism among heroin addicts in California in the early 1980s. This outbreak was linked to MPTP, a chemical compound that had been inadvertently synthesized in the process of heroin production. Further biochemical studies with MPTP demonstrated that a MPTP metabolite can selectively inhibit mitochondrial complex I in dopaminergic neurons and induce acute PD-like symptoms in experimental animals. This evidence was used to develop an animal model of PD. However, the MPTP model does not show the accumulation of Lewy bodies or the systemic inhibition of complex I seen in idiopathic PD in humans. To develop a more accurate animal model of PD, Betarbet and colleagues exposed rats to rotenone, a widely used pesticide derived from the roots of certain plant species. Rotenone-treated rats developed bradykinesia, rigidity, postural instability and a resting tremor that improved with administration of a dopamine analog. Additionally, brain sections from these rats demonstrated progressive degeneration of the substantia nigra, and the surviving nigral neurons showed cytoplasmic inclusions that resembled Lewy bodies. Rotenone administration also produced complex I inhibition throughout the brain. Interestingly, Betarbet and colleagues observed PD-like symptoms at concentrations of rotenone that were insufficient to significantly impair oxidative phosphorylation throughout the brain. They speculate that this finding argues against ATP depletion as a mechanism for the loss of dopaminergic neurons in PD and supports the theory that free radicals, generated from mitochondrial inhibition, may be responsible for the damage. From an epidemiological perspective, these findings also suggest that low levels of environmental rotenone, and other environmental toxins that inhibit mitochondrial complex I, may contribute to the pathogenesis of idiopathic PD.

Betarbet R, Sherer TB, MacKenzie G, *et al.* (2000). *Nature Neuroscience*. 3: 1301-6.

Prolific Scientist Profiles

An Interview with Dr. Charles Tator

Christopher J. Hall, BSc., (OT3)



The heavy morbidity of spinal cord injuries is well known to both physicians and the general public. With such a reputation, it should come as no surprise that these injuries have attracted the interest of many researchers around the world, challenging the medical profession with one of its greatest unconquered frontiers. Among the world leaders in this field of research is Dr. Charles Tator, Professor and Past Chair of Neurosurgery at the University of Toronto, and President of the Think First Foundation of Canada.

A Toronto native who completed his medical and research training in this city, Dr. Tator has compiled a staggering collection of accolades throughout his impressive career as both physician and researcher. Dr. Tator's achievements have been recognized by many organizations, including St. John's Ambulance, the Rick Hansen Man in Motion Foundation and the Royal Life Saving Society of Canada. He was the first neurosurgeon to receive the Heiner Sell Distinguished Scientist Award of the American Spinal Injury Association and the first Canadian to be elected Chair of the Joint Section on Neurotrauma and Critical Care of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. In 1997, he received the Lifetime Achievement Award of the Canadian Brain Injury Coalition and, in 1999, he was awarded the Alan R. Hudson Teaching Award from the University of Toronto for his contribution to undergraduate and postgraduate teaching. He was also named a Member of the Order of Canada in January, 2000.

Dr. Tator has published 237 papers, 30 book chapters and 150 abstracts, mostly in the field of acute spinal cord injury. His current research focuses on the mechanisms and treatment of neuronal, axonal, and vascular injuries of the spinal cord and utilizes specific *in vivo* methods, including measurement of blood flow and evoked potentials, intracellular calcium measurements, assessment of axonal tracers, and behavioural assessment. He is also utilizing an *in vitro* model of neurite injury to study axonal regeneration. The treatment strategies he is pursuing include calcium channel blockers and calcium buffers, growth factors to induce cellular proliferation, and axonal regeneration and transplantation. Dr. Tator is also involved in studies of the treatment, epidemiology and prevention of neurotrauma in patients, especially those with injuries in sports and recreation.

N&V: What first drew you to the field of neurosurgery?

CT: I loved the brain, right from the start. My first intentions were to enter the field of psychiatry, but during the first-year [neuroanatomy] course in medical school, I discovered that nobody talked about the locations of the id, the ego, the superego, etc. This disappointed me, since I had imagined that the mind would be much clearer, and I discovered that we didn't know very much about it after all. This fueled a desire in me to discover how the brain worked, and I felt this was the area in which I wanted to make my contribution to the world of medicine. That neuroanatomy course, with its talented and inspiring lecturers, really played a key role in my decision to enter the field of neuroscience.

N&V: Was it always your intention to become both a physician and a researcher?

CT: Yes it was, from the very beginning of my education. Even before my clinical training as a neurosurgeon had begun, I entered into a three-year period of training in research. My early areas of interest included brain tumor research, and this changed gradually over time to include spinal cord injuries. I eventually discovered that having two major areas of interest was compromising my ability to produce quality research in both of them, so I made a choice to concentrate on the spinal cord.

N&V: How much time do you devote to research versus clinical practice?

CT: I would say that it's about a 50-50 split. I've always felt that it is practically impossible to retain a high level of surgical skill and clinical acumen if less than half of your time is spent in clinical practice. This is probably not true for all specialties; surgery in particular demands that you retain your manual skills by constantly exercising them. Involvement in research, on the other hand, is a personal decision. There are many neurosurgeons who are very talented and very competent in their areas of expertise, but who perform little to no research at all. It is my opinion, however, that they are not very likely to become innovators in this field of medicine; to do so requires a fairly steady commitment to research. For me personally, contributing to the body of knowledge that the practice of medicine is based upon is a very important part of my role as a neurosurgeon, and thus

I commit as large a portion of my time to research as I feel is possible.

N&V: The primary goal of your research is to find a way to regenerate damaged spinal cord tissue. Would you care to comment on the current state of advancement of research in this area?

CT: Around the world, there are about ten major strategies currently under investigation that possess any real potential to improve the ability of spinal cord tissue to regenerate. Canadian neuroscience researchers in general have been world leaders in these areas and have contributed significantly to them. In our lab specifically, we are currently working with three of these ten strategies; unfortunately, despite the many gains in knowledge that we have made over the years, we are still unable to regenerate spinal cord tissue in a clinical setting.

N&V: Does the high quality of Canadian neuroscience research help you to resist the call of more lucrative opportunities south of the border?

CT: It certainly does. I actually have a drawer full of offers for employment in the United States, but there is a relative deficit of neurosurgeon-researchers in that country compared to this one. In other words, Canadian neurosurgery programs have generated a large number of people with dual training in both the clinical and research aspects of this specialty, especially here at the University of Toronto. Furthermore, Canadian neuroscience researchers enjoy the same level of international recognition as their American colleagues, and there is a free flow of ideas across the border, thus making your country of residence a matter of relatively little importance in that sense. On top of this, I was born in Toronto, and I really enjoy living here, as does my wife. I realize that moving to the United States might provide me with a significantly higher income, and I suppose that the research grants made available to researchers are much more impressive in that country. On the other hand, there are a number of negative lifestyle changes that would result from such a relocation, which would more than offset the gains to be made. Perhaps the only major complaint I have as a Canadian researcher is that we do not receive the same level of financial support from our government as the American researchers do from theirs. Both the provincial and federal levels of government in this country consistently lag behind the United States government in their commitment to funding researchers, which has an obvious effect on our ability to produce quality research.

N&V: You are also involved in setting standards for hockey leagues to help prevent head injuries. How did your involvement in this project come about?

CT: [My involvement began] largely as a product of the rash of head and spinal cord injuries we were seeing in this sport 20 years ago. I have always been interested in curing spinal cord injuries, but it has occurred to me that we will probably not achieve this goal in my lifetime. As mentioned before, we still cannot restore a quadriplegic person's ability to walk again. We can, however, prevent the occurrence of spinal cord injuries. For these reasons, we began a registry to track the ways in which players were sustaining these injuries in

hockey rinks across the country. Over the years, we discovered that being hit from behind while standing near the boards was the most common mechanism of spinal cord injury in hockey. From here we were able to convince the Canadian Amateur Hockey Association to institute a rule in the mid-1980s that would punish players for hitting their opponents from behind. This was the first rule of its kind in Canada, and it was complimented with a video we produced which was to be shown to all players at the beginning of every season to educate them about safe ways to play the game. Since having instituted this rule, we have noticed a steady decline in the number of spinal cord injuries suffered by hockey players, though we have by no means eliminated them from the game completely. Unfortunately, concussions are still a prominent neurological injury among hockey players today, and the focus of our research and prevention programs has now shifted towards addressing this.

N&V: Taking on the responsibilities of both a researcher and a clinician must leave you with precious little free time. What kind of activities, if any, are you able to enjoy outside the world of medicine?

CT: Looking back, I realize that my career has been a very time consuming endeavour, leaving me very little free time to spend with my family or pursuing my interests outside of medicine. This is an unfortunate and significant side effect of having a dual career, and it is generally unavoidable for those of us who wish to play the role of both clinician and researcher. In spite of my demanding schedule, however, I do occasionally find time to enjoy my other interests. I really enjoy listening to classical music, and I attend performances by the Toronto Symphony Orchestra when I can. I also have a cottage in Algonquin Park, and during the summer I usually take one month away from work to spend up there with my family, which I find to be a particularly relaxing experience. Finally, as you might already have guessed, I also have an interest in hockey, which has played a role in motivating some of my current research endeavours. I used to play for the medical school intramural team during my time as a medical student and, fortunately, I can still find the time to go to the occasional professional hockey game here in Toronto.

N&V: It sounds as though you consider a strong sense of commitment and dedication to be an essential character trait in a neurosurgeon.

CT: Yes, I do. Naturally, becoming any kind of doctor requires a significant amount of personal commitment, even after your training is completed. However, neurosurgery in particular is very demanding in this regard. We regularly remind applicants to our residency training program that entering into this specialty of medicine will almost certainly obligate them to sacrifice the majority of their free time. It is definitely not advisable to enter into a career in neurosurgery, especially one that includes research, if it is your desire to have lots of free time outside of medicine. Having said that, I should also express my belief that it is a very rewarding specialty, and one which I enjoy very much.

Back to Basics V

An Approach to the Patient with a Life-Threatening Acid-Base Disturbance: The Acidemias

Manish Shah, B.Sc. (OT3)
Murray Beuerlein, M.Sc. (OT3)
Karoan Danayan, B.Sc. (OT4)

This article, the first installment of a two part series that will address acid-base disturbances, discusses those conditions that result in acidemia – metabolic and respiratory acidosis. The second installment will address those conditions that result in alkalemia – metabolic and respiratory alkalosis – as well as mixed acid-base disturbances.

Disturbances of acid-base homeostasis are caused by a large number of medical conditions, and patients with such disturbances are encountered on a regular basis. However, relative to the total number of conditions that can result in an acid-base disturbance, the number that pose an immediate risk to the patient's life is very small. Identification of these life-threatening conditions is extremely important if they are to be managed quickly and appropriately, and thus, the emphasis of this article is on the identification of life-threatening situations.

It is important to note that although an acidemia can potentially cause life-threatening changes in organ and tissue function, it is usually the underlying cause rather than the acidemia itself that is life-threatening. In many cases, the disturbance in acid-base homeostasis simply serves as a symptom of the underlying condition and the nature of this disturbance often provides clues that point to a particular underlying cause.

The goal of this article is to provide a systematic approach to acid-base disturbances, specifically those that result in acidemias, such that the disturbance, and more importantly, the underlying cause can be appropriately identified.

Background

Addition of H⁺ to the Body Equals the Addition of Anions

Relative to other major ions in the body such as Na⁺, K⁺, or HCO₃⁻, the concentration of H⁺ ([H⁺]) is almost a million-fold lower (Table 1). However, control of the [H⁺] within a narrow range is essential for the normal function of proteins. If the [H⁺] rises, H⁺ will bind avidly to proteins, which can result in changes in protein structure, and thus, protein function.¹

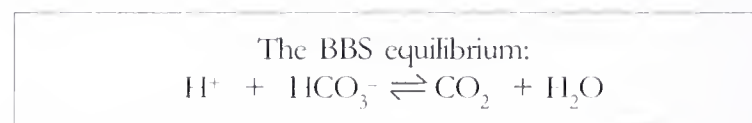
During daily metabolism, H⁺ are added to the body along with their conjugate base (an anion). However, metabolism of these anions to neutral end-products or excretion with H⁺ or NH₄⁺ in the urine prevents their accumulation in the body and, thus, prevents the net production of H⁺. Accumulation of these anions may occur if their production rises dramatically or if they cannot be metabolized or

excreted (due to liver or kidney disease, respectively). In addition, there are certain anions that the body cannot metabolize to neutral end-products and that cannot be excreted with H⁺ or NH₄⁺.

The presence of these anions in plasma is a sign that there has been net production of H⁺. Their presence is of clinical significance because they provide diagnostic clues that may point to the underlying cause of the acidemia, and because some of these anions are potentially toxic.

Buffering: Preventing Binding of H⁺ to Intracellular Proteins

Binding of H⁺ to intracellular proteins could have the deleterious results mentioned above. Thus, the bicarbonate buffer system (BBS) – described by the equilibrium shown below – has the important function of preventing H⁺ from binding to intracellular proteins.



The BBS carries out this important function by minimizing the change in the [H⁺] and is able to do so by controlling the pCO₂. When the pCO₂ is decreased (via increased alveolar ventilation), the BBS equilibrium shifts such that H⁺ and HCO₃⁻ are consumed, while an increase in pCO₂ (via decreased ventilation) has the opposite effect. Thus, when there has been net addition of acid to the body, the BBS can effectively force the excess H⁺ to react with HCO₃⁻ by inducing hyperventilation to lower the pCO₂.

If the acid-base disturbance is marked the BBS may no longer be able to control the [H⁺], resulting in binding of H⁺ to intracellular proteins. These situations can be exacerbated if the pCO₂ cannot be regulated, such as when there is impaired ventilation or decreased blood flow.

Regeneration of HCO₃⁻ Involves Excretion of NH₄⁺

The H⁺ produced during daily metabolism or due to a pathological disturbance are removed by a process that consumes HCO₃⁻, as described above. The HCO₃⁻ must be replaced and it is the kidney that carries out this function, largely by the excretion of NH₄⁺ in the

urine. Glutamine is broken down into HCO_3^- and NH_4^+ in epithelial cells lining the proximal convoluted tubule (PCT), and HCO_3^- enters the circulation. The process of HCO_3^- regeneration is controlled by the intracellular pH of the PCT cells (intracellular acidosis promotes glutamine breakdown) and by the excretion of NH_4^+ (impaired excretion prevents the net addition of HCO_3^- to the circulation).

Systematic Approach to Identification of an Acid-Base Disturbance

Identifying the type of acid-base disturbance present and determining the underlying cause of this disturbance requires a systematic approach to ensure that important aspects are not overlooked. We suggest the approach outlined in Table 2, which is described in more detail below.

Step 1 – Establish the Clinical Context

An assessment of the clinical situation will provide an indication of the urgency of the patient’s condition. Additionally, a careful history and physical examination, along with examination of past medical records, is essential because the clinical information obtained can be extremely valuable in determining the underlying cause of the disturbance. The extent of this assessment must be appropriate for the urgency of the clinical situation.

Step 2 – Examine the four major lab measurements – pH, PaCO_2 , $[\text{HCO}_3^-]$, and Plasma Anion Gap

Examining these four parameters allows one to identify and characterize the primary acid-base disturbance and identify the presence of concurrent secondary disturbances (mixed acid-base disorders).

(i) Identifying the primary disturbance

Begin by identifying the most abnormal value, which will provide direction as to which disturbance is present. Changes in the pH clearly identify acidemias versus alkalemias, and large changes in the $[\text{HCO}_3^-]$ are suggestive of metabolic disorders. Examination of all values together will then allow you to confirm which disorder is present (Table 3).

(ii) Using the Plasma Anion Gap

An increased plasma anion gap (PAG) is usually a sign that there has been overproduction, addition, or retention of an acid in plasma. The “gap” increases because of the presence of the acid’s unmeasured conjugate base (an anion) in plasma.

Examining the PAG in patients with a metabolic acidosis is useful, as it helps to narrow the differential diagnosis (see the discussion of metabolic acidoses below). If the PAG is increased, it should be compared with the change in $[\text{HCO}_3^-]$. For every 1 mEq/L of conjugate base anion present in plasma, one expects a 1 mEq/L increase in the PAG and a 1 mmol/L decrease in $[\text{HCO}_3^-]$. If the difference in magnitude of rise in PAG compared with the magnitude of the fall in $[\text{HCO}_3^-]$ is greater than 5 mmol/L, this suggests that a second disturbance is present.

The PAG should, however, be examined with all acid-base disturbances. An increased PAG may be the only clue that there is an acid-base disturbance present (i.e., in a mixed acid-base disturbance with a normal pH). Additionally, in a patient with a primary acid-base disturbance other than metabolic acidosis, an increased PAG suggests the presence of a concurrent metabolic acidosis.

Table 1
Normal Laboratory Values

	Normal value	Units
Arterial blood gases (ABG)		
pH	7.38 – 7.42	
PaCO_2	37 – 43	mmHg
PaO_2	90 – 100	mmHg
SaO_2	95 – 98 %	
$[\text{HCO}_3^-]$	22 – 28	mmol/L
$[\text{H}^+]$	38 – 42	nmol/L
Serum electrolytes		
$[\text{Na}^+]$	135 – 145	mmol/L
$[\text{K}^+]$	3.5 – 5.1	mmol/L
$[\text{Cl}^-]$	98 – 106	mmol/L
Osmolality	280–300	mOsm/kg

Table 2
Systematic Approach to the Identification of an Acid-base Disturbance

Step 1:	Establish the Clinical Context
Step 2:	Examine the four major lab measurements – pH, PaCO_2 , $[\text{HCO}_3^-]$, and Plasma Anion Gap
Step 3:	Examine other lab measurements

Table 3
Characteristics of the Different Acid-base Disturbances

Disturbance	Identifying Characteristics
Metabolic Acidosis	1. Low pH 2. Low $[\text{HCO}_3^-]$
Respiratory Acidosis	1. Low pH 2. High PaCO_2
Metabolic Alkalosis	1. High pH 2. High $[\text{HCO}_3^-]$
Respiratory Alkalosis	1. High pH 2. Low PaCO_2

(iii) Examining the expected physiological response

A primary disturbance results in a physiological response by the body which attempts to return the $[\text{H}^+]$ towards normal. Particular responses are expected and if the observed response is inadequate or inappropriate, this may indicate the presence of a secondary disturbance (Table 4).

Step 3 – Examine other lab measurements

Measurements such as the plasma osmolal gap (POG), urine electrolytes, urine osmolal gap, urine net charge, and urine pH may be useful in determining the underlying cause of the acid-base disturbance. The uses of these measurements are outlined in Table 5 and are described in more detail in the appropriate sections of this article.

Table 4
Expected Physiological Responses to Each Acid-base Disturbance

Primary Disturbance	Expected Response	
	Mechanism	Magnitude
Metabolic Acidosis	Hyperventilation	For each 1 mmol/L decrease in $[\text{HCO}_3^-]$, the PaCO_2 should decrease by 1 mmHg.
Respiratory Acidosis	Acute: shift in the BBS to produce more HCO_3^-	For each 10 mm Hg rise in the PaCO_2 , the $[\text{HCO}_3^-]$ should rise by 0.8 mmol/L
	Chronic: renal generation of HCO_3^-	For each 10 mm Hg rise in the PaCO_2 , the $[\text{HCO}_3^-]$ should rise by 3 mmol/L

Table 5
Useful Measurements for the Analysis of Acid-base Disturbances

Measurement	Equation	Normal Value	Use
$[\text{H}^+]$	For every 0.1 unit increase in the pH above 7.0, multiply 100 nmol/L by 0.8	For pH = 7.40, $[\text{H}^+] = 40 \text{ nmol/L}$	Calculating the $[\text{H}^+]$ from the reported pH
Plasma Anion Gap (PAG)	$[\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$	$12 \pm 2 \text{ mEq/L}$	Detects the accumulation of acids in plasma (excluding HCl and H_2CO_3)
Plasma Osmolal Gap (POG)	Measured Osmolality – Calculated Osmolality Calculated Osmolality = $2[\text{Na}^+] + [\text{Glucose}] + [\text{Urea}]$	$< 10 \text{ mOsm/L}$	Detects the presence of alcohols in plasma
Urine Osmolal Gap (UOG)	Measured Osmolality – Calculated Osmolality Calculated Osmolality = $2([\text{Na}^+] + [\text{K}^+]) + [\text{Glucose}] + [\text{Urea}]$	See text	Yields an estimate of the $[\text{NH}_4^+]$ in urine
Urine pH	Measured value	—	Detects a deficit in renal NH_3 production and/or H^+ secretion

Metabolic Acidosis

Definition

Metabolic acidosis is characterized by low $[\text{HCO}_3^-]$ and an acidic pH. The causes of metabolic acidosis can be classified into three broad categories: (A) overproduction of acid, (B) direct loss of sodium bicarbonate, and (C) indirect loss of sodium bicarbonate due to a failure to excrete NH_4^+ in the urine.

A. Overproduction of Acid

Acids are continuously being produced and metabolized within the body. Under normal circumstances, the body is able to metabolize these acids and maintain homeostasis. However, if acid production is increased or if their removal is compromised, a metabolic acidosis will ensue.¹ Metabolic acidoses due to overproduction of acids are usually associated with an elevated plasma anion gap (Table 6).

1. L-Lactic Acidosis

Cause

Lactic acidosis is commonly classified as Type A, due to tissue hypoxia, and Type B, resulting from compromised metabolism of

lactate.¹ In general, only Type A lactic acidosis represents a medical emergency that must be dealt with promptly. The hypoxia may be caused by hypoxemia, hypotension, or impaired blood supply to an organ. Of these, lack of cardiac output (i.e., cardiogenic shock) is the most important. The lack of O_2 necessitates anaerobic production of ATP from glucose with the formation of lactic acid. In normal circumstances, tissue perfusion will carry CO_2 away from its site of production to the lungs to be eliminated. However, in a hypoperfused state such as cardiogenic shock, decreased tissue perfusion requires a high $[\text{CO}_2]$ to achieve CO_2 removal. As a result, $[\text{CO}_2]$ rises locally, causing the BBS to fail, and obligates intracellular buffering of the H^+ by proteins.

If the tissue can be re-perfused with oxygenated blood, lactic acid production will cease upon oxygen availability, and the BBS will be able to buffer the acid as a result of CO_2 removal. Furthermore, the circulating lactate will be slowly metabolized in the liver and kidney with the removal of the H^+ that had been introduced.

Identification

Lactic acidosis is accompanied by a plasma anion gap due to the presence of lactate but without any increase in the POG. The physiological response (hyperventilation) is usually adequate, unless the

source of the hypoxia was primarily a failure of the lungs to begin with.

The clinical presentation of lactic acidosis is variable and depends on the exact cause underlying the hypoxia. Clinical features may include circulatory collapse, cardiogenic shock, focal signs of ischemia in one region of the body, sepsis, or signs of low oxygen content such as cyanosis or severe anemia.²

Table 6
Plasma Anion Gap Metabolic Acidosis

- A. Over Production of Acid
1. L-Lactic acidosis

2. D-Lactic acidosis

3. Diabetic ketoacidosis

4. Alcoholic ketoacidosis

5. Methanol intoxication

6. Ethylene glycol intoxication
- B. Renal failure – failure to excrete acids

Management

The key to treating Type A lactic acidosis is to restore circulation to the tissues in order to match oxygen delivery with demand. This is accomplished by treating the underlying disorder causing the hypoxia.

In the situation of circulatory collapse, blood pressure elevation is essential. This can be achieved with the infusion of blood, plasma or normal saline depending on the exact etiology. Other means of increasing tissue oxygenation include providing a high inspired O₂ fraction, ventilator support, and inotropic drugs such as dopamine or dobutamine.³ NaHCO₃ treatment is rarely indicated in Type A lactic acidosis because the rate of acid production is usually too high for the NaHCO₃ to impact the system.

2. D-Lactic Acidosis

Cause

Certain GI bacteria convert carbohydrates to organic acids such as D-Lactic acid. Three factors can promote the increased production of D-lactic acid by these bacteria. First, antibiotics can inhibit the normal endogenous flora and allow D-lactic acid-producing bacteria to proliferate. Second, delayed GI motility allows the bacteria prolonged exposure to ingested carbohydrates, and enhances acid production. Third, a diet rich in carbohydrates provides additional substrate for the bacteria to convert into organic acids. In addition to the production of organic acids, these bacteria also produce amines, which result in CNS manifestations.¹

Identification

D-lactic acid produces an anion gap metabolic acidosis. Central nervous system manifestations resulting from amine production include cerebellar dysfunction leading to changes in gait, as well as personality changes and confusion. If D-lactic acidosis is suspected, the presence of the risk factors (antibiotics, delayed motility, and carbohydrate rich diet) should be assessed. An assay specific for D-lactate can confirm the diagnosis.

Management

Treatment focuses on the GI problem. First, the source of carbohydrate should be stopped. With the removal of substrate, bacterial production of amine neurotoxins will decrease, as will production of D-lactate. Second, GI motility should be re-established to decrease the amount of time the carbohydrate substrate is available for bacterial digestion.

3. Ketoacidosis

Cause

Ketoacidosis results from a relative insulin deficiency that activates hormone sensitive lipase (HSL), an enzyme responsible for the conversion of triglycerides (TG) to free fatty acids. The intermediate, β-hydroxybutyrate, can be oxidized by either the brain or the kidney to generate ATP.



Two specific examples of ketoacidosis are diabetic ketoacidosis (DKA) and alcoholic ketoacidosis (AKA). In DKA the primary cause is a lack of insulin due to failure of the pancreatic β-cells; this is most commonly seen in children presenting with insulin-dependent diabetes mellitus. In AKA, the insulin deficiency is due to profound volume depletion after significant alcohol intake, caused by excessive vomiting and subsequent increase in adrenergic tone.

Identification

The principal clinical features of ketoacidosis are shown in Table 7. DKA can be diagnosed in individuals with a plasma anion gap metabolic acidosis and the mentioned signs with positive tests for hyperglycemia, ketonemia and a suspicion of Type I diabetes.⁴ Deficiency in insulin may result in moderate hyperkalemia due to decreased uptake of potassium into the cell, however the overall body composition of potassium is reduced due to osmotic diuresis.

Table 7
Clinical Features of Diabetic Ketoacidosis

1. Young age of patient
2. Shock
3. "Fruity" smell of acetone on breath
4. Kussmaul respirations
5. Polyuria and polydipsia

Patients with alcoholic ketoacidosis are severely ECF volume-contracted.¹ In addition, acute alcohol consumption will be revealed upon history taking and there may be a normal pH due to loss of stomach acid with vomiting. In contrast to DKA, the potassium concentration may not to be elevated in AKA, due to renal loss of potassium in response to emesis. A normal serum [K⁺] in these patients is a sign of a profound deficit in total body potassium. The plasma osmolal gap will be elevated in these patients due to the presence of ethanol in the blood.

Management

The management of DKA involves (1) infusion of normal saline to restore ECF volume (2) curtailing the rate of acid production by

administration of insulin, and (3) replacement of total body K^+ . The administration of potassium is important because insulin causes potassium to enter cells. Without potassium infusion, a potentially life-threatening hypokalemia could result.

Management of DKA focuses on the restoration of ECF volume and K^+ deficit. Once the ECF volume is returned to normal, the adrenergic stimulation that generated the insulin deficiency is removed and acid production ceases on its own without the need for insulin administration.

4. Methanol and Ethylene Glycol Poisoning

Cause

Methanol and ethylene glycol are not directly toxic themselves, but they are metabolized to acids within the liver, and it is these acids that impart the toxic effects.

- methanol $\rightarrow$ formaldehyde $\rightarrow$ formic acid
- ethylene glycol $\rightarrow$ glycoaldehyde $\rightarrow$ glycolic acid
 $\rightarrow$ glyoxylic acid $\rightarrow$ oxalic acid

The conversion of methanol and ethylene glycol to formaldehyde and glycoaldehyde, respectively, is carried out by the enzyme alcohol dehydrogenase, which also converts ethanol to acetaldehyde.

Identification

Methanol and ethylene glycol poisoning are considered together because of the similarities in their clinical presentation and laboratory values. Both produce a plasma anion gap metabolic acidosis with a rise in the plasma osmolal gap; the POG is increased as a result of the alcohols in the blood.

Methanol is found in products such as paints, cleaners, and windshield washer fluid. Ethylene glycol is a component of anti-freeze solutions. Both of these compounds may be ingested as an inexpensive and readily available ethanol substitute by individuals with chronic alcohol addiction, or as a means of suicide.

Table 8
Clinical Features of Ethylene Glycol Poisoning

1. Commonly seen in individuals with addictions to ethanol
2. Symptoms develop 6-12 hours after ingestion
3. CNS depression (similar to ethanol intoxication)
4. Kussmaul respiration
5. Urine oxalate crystals

Table 9
Clinical Features of Methanol Poisoning

1. Commonly seen in individuals with addictions to ethanol
2. Symptoms develop 10-30 hours after ingestion
3. CNS depression (similar to ethanol intoxication)
4. Visual disturbances – such as blurred vision, diplopia, or complete visual loss
5. Aromatic odor of methanol on breath

Differentiation between these two can be made definitively with a specific assay. However the clinical clues presented in Tables 8 and 9 can help make the clinical diagnosis. In general, ethylene glycol intoxication may be suspected after an episode of drunkenness when coma and Kussmaul respiration are seen in the context of a metabolic acidosis with elevated anion and osmolal gaps.⁵ Methanol poisoning should be suspected in patients who present with visual symptoms or unexplained coma or seizure in the presence of a metabolic acidosis with elevated anion and osmolal gaps.^{6,7} The consequences of intoxication with the acid metabolites are severe CNS toxicity and acute tubular necrosis, in the case of ethylene glycol poisoning, and CNS toxicity with specific damage to the optic nerve in the case of methanol poisoning.

Management

The strategy for treating these patients is through inhibiting the conversion of the ingested compound to their toxic metabolites. This is accomplished in both cases with the administration of an alcohol dehydrogenase inhibitor. Classically, ethanol has been used; however, fomepizole (4-methylpyrazole) has become available recently. Fomepizole has clearly validated efficacy, predictable pharmacokinetics, is easy to administer, and has no major adverse reactions.⁸ The formate or glycolate that has already been produced, along with the remaining alcohol, can be removed from the circulation by dialysis.

5. Toluene Intoxication

Cause

Toluene is a solvent found commonly in glue. Upon inhalation, toluene is metabolized by the liver:

- toluene $\rightarrow$ benzoic acid $\rightarrow$ hippurate⁻ + H^+

Identification

Unlike other metabolic acidoses caused by the overproduction of acid, toluene inhalation does not routinely produce a plasma anion gap, because the conjugate base (hippurate) is not retained in the plasma. Instead, if renal function remains normal, hippurate is excreted by the kidneys. An increased urine osmolal gap will confirm the presence of hippurate and its counter-ion.

Toluene intoxication is most commonly seen in the homeless population. Because of the poor nutritional status of these individuals and the loss of K^+ and Na^+ as the counter-ions for hippurate in the urine, they are often ECF volume-depleted and hypokalemic. Tachyarrhythmias are the classical manifestations of toluene cardiotoxicity. This is thought to result from toluene-induced sensitization of the myocardium to the arrhythmogenic effects of endogenous catecholamines.⁹

Management

The management of toluene inhalation focuses on the restoration of K^+ and ECF volume with normal saline. $NaHCO_3$ is not usually administered because of the possible exacerbation of hypokalemia. In fact, the acidemia usually resolves spontaneously within a few days.

B. Direct Loss of Sodium Bicarbonate

Cause

Direct loss of sodium bicarbonate from the body is not common. Causes include severe diarrhea, and loss of sodium bicarbonate in the urine due to failure of proximal tubular H^+ secretion. The latter condition is referred to as proximal renal tubular acidosis (pRTA), and is one component of Fanconi syndrome.

Identification

In order to cause clinically significant metabolic acidosis, the volume of diarrhea must approach 4-5 litres per day. These patients develop a life-threatening hypovolemia before any significant acidosis arises.

Proximal renal tubular acidosis produces a normal anion gap metabolic acidosis. Examination of the urine reveals significant bicarbonaturia, and the urine osmolal gap identifies the fact that relatively little NH_4^+ excretion is taking place.

Management

Direct loss of sodium bicarbonate rarely results in an emergent metabolic acidosis. As with most causes of metabolic acidosis, treatment of the underlying disorder is the standard of care in these situations.

C. Indirect Loss of Sodium Bicarbonate – Failure to Excrete NH_4^+ in the Urine

Cause

Distal renal tubular acidosis (dRTA) is a condition characterized by failure of the kidneys to make new HCO_3^- due to an inability to excrete NH_4^+ in the urine. Within the family of conditions characterized by failure to excrete NH_4^+ , the defect can be localized to either the production of NH_3 , or secretion of H^+ by the proton pump in the collecting duct. Specific causes of dRTA include renal failure, hyperkalemia, and medullary interstitial disease; other causes are outlined in Table 10.

Table 10
Normal Anion Gap Metabolic Acidosis

- A. Direct loss of bicarbonate
1. Severe diarrhea

2. Bicarbonaturia

• Acetazolamide ingestion
- B. Failure to make new bicarbonate
1. Failure to make NH_3

• Low GFR – e.g. renal failure

• Hyperkalemia

• Medullary interstitial disease
2. Failure of distal H^+ secretion
- Sjogren's syndrome
- Amphotericin B

Identification

Loss of sodium bicarbonate yields a normal anion gap metabolic acidosis. Identification of the underlying cause of sodium bicarbonate loss is aided by examination of the urine osmolal gap (UOG). The UOG is used to determine the amount of NH_4^+ being secreted by the kidney in the urine. The $[\text{NH}_4^+]$ is estimated as $1/2$ UOG. Normally the UOG is 400 mOsm/kg or greater, which corresponds to an $[\text{NH}_4^+]$ of 200 mmol/L. In dRTA, the UOG will be less than 100 mOsm/kg, which correlates to a urine $[\text{NH}_4^+]$ of 50 mmol/L. In the presence of a UOG less than 100 mOsm/Kg, the urine pH can provide more information about the cause of the disorder. A urine pH > 6.5 points to failure of H^+ secretion, whereas a pH < 5.0 indicates that the proton pump is functional and the deficit is related to NH_3 formation. If the urine pH falls between 5.0 – 6.5, a dual problem may be suspected.

The key feature in identifying renal failure as a cause of a normal

anion gap metabolic acidosis is a large increase (5-10 fold) in serum creatinine and BUN levels. In addition, patients in this condition have a potentially life-threatening hyperkalemia, and are ECF volume expanded.

Management

There are many causes of renal tubular acidosis, and the treatment is specific to each. One key example is failure of the distal tubular H^+ pump, which can occur in Sjögren's syndrome. This condition is associated with a potentially life-threatening hypokalemia, which is treated with potassium infusion. Administration of exogenous NaHCO_3 will shift K^+ into the cells and exacerbate the hypokalemia, and is therefore contraindicated. Furthermore, hypokalemia can produce muscle fatigue leading to an insufficient respiratory effort. The PaCO_2 should be followed in these patients to assess the adequacy of their respiratory effort. If the appropriate physiological drop in PaCO_2 is not being achieved, the patient may need assistance with ventilation.

Dialysis is the cornerstone of management of renal failure-induced metabolic acidosis. Sodium bicarbonate is contraindicated, as it may further expand ECF volume in these patients and lead to pulmonary edema.

Respiratory Acidosis

Respiratory acidosis arises due to decreased ventilation, which results in a higher than normal PaCO_2 . The increased PaCO_2 shifts the BBS such that the production of HCO_3^- and H^+ is increased. This results in an acidemia, despite the fact that HCO_3^- and H^+ are produced in equimolar amounts, because the relative concentration of HCO_3^- is much higher than that of H^+ (Table 1). Overproduction of CO_2 may coexist with hypoventilation in certain situations, but is never the sole explanation for a respiratory acidosis. This is because the normal respiratory system is stimulated by increased pCO_2 to increase ventilation.

There is a wide range of conditions, both acute and chronic, that result in decreased ventilation and thus, respiratory acidosis (Table 11). However, only a handful of acute situations pose an immediate risk to the patient's life. Chronic causes of respiratory acidosis, such as chronic obstructive pulmonary disease (COPD), do not pose an immediate risk unless they have been exacerbated by an acute event such as pneumonia, pulmonary edema, or the acute events mentioned below. In these cases, the acute exacerbation should be treated with the goal of returning the patient to their previous state of chronic acidosis.¹⁰

The urgent situations described below can lead to severe hypercapnia and resultant hypoxemia, posing a major threat to the patient's life. Rapid diagnosis of the underlying cause is essential if appropriate management is to be initiated. Management involves treating the underlying cause; however, if these measures do not suffice to remove the patient from immediate danger, additional measures such as supplemental oxygen and assisted ventilation may be required.

1. Airway Obstruction

Causes

Obstruction can be the result of aspiration of a foreign body or vomitus, or status asthmaticus.

Identification

The clinical presentation of the patient (history, signs of respiratory distress, etc.) will yield the important information required to make the correct diagnosis of airway obstruction.

Management

The goal in this situation is to restore ventilation by removing the obstruction. Foreign bodies or vomitus in the airway should be

Table 11
Conditions that can cause a respiratory acidosis¹

Patients who are unable to breathe (respiratory or muscular disorders)	Patients who will not breathe (impaired neurological input)
- Myasthenia - Relaxant drugs - Muscular dystrophy - Muscle fatigue or paralysis - Interstitial lung disease - Pulmonary fibrosis - Asthma - Bronchitis - Emphysema - Upper airway obstruction	- Post-hypoxic brain damage - Cerebral trauma - Intracranial disease - Psychotropic drugs - Brain stem herniation - Encephalitis - Central sleep apnea - Severe metabolic alkalosis - Drugs (sedatives, narcotics) - Bulbar palsy - Anterior horn cell lesions - Disruption of airway

removed with abdominal thrusting or suction, respectively.¹⁰ Status asthmaticus should be treated appropriately with bronchodilators, intravenous steroids, and oxygen administration.¹¹

2. Hypokalemic distal RTA

Cause

Distal RTA is discussed above in more detail, in the section describing the causes of metabolic acidosis. Relevant to respiratory acidosis, this condition can produce significant hypokalemia, which may result in respiratory muscle fatigue and thus, poor respiratory effort.

Identification & Management

The identification and management of distal RTA is discussed in more detail in the metabolic acidosis section; however, it is important to remember that the potassium depletion must be corrected and that NaHCO_3 administration is contraindicated.

3. Acutely impaired ventilatory drive

Causes

Ventilatory drive can be reduced due to an overdose of CNS-depressing drugs. CNS activity can be decreased such that respiratory drive is blunted; in severe situations, this depression may result in apnea.

Patients with COPD, who have chronic hypercapnia due to hypoventilation, can lose their ventilatory drive when oxygen is administered. Normally, the major central stimulus for ventilation is an increase in plasma $[\text{H}^+]$ concentration, which in the case of respiratory acidosis, is a direct reflection of the PaCO_2 . Decreases in the PaO_2 (hypoxia) also stimulate ventilation via peripheral receptors; however, their role is relatively minor in comparison to PaCO_2 . In patients with chronic hypercapnia, the central receptors effectively become less sensitive to changes in the PaCO_2 , and hypoxia becomes the major stimulus to breathe. Thus, if these patients are given high concentrations of supplemental oxygen, they may lose their ventilatory drive.

Identification

Identification of patients who have a drug overdose is based upon obtaining a history (if possible), looking for signs of specific toxidromes, and conducting appropriate laboratory investigations. However, these must be appropriate for the urgency of the clinical situation.

Patients with COPD who are given high concentration supplemental oxygen become hypercapnic from hypoventilation and may show

signs of decreasing level of consciousness (LOC). When the hypoxic drive to breathe is lost completely, the patient may become apneic.

Management

Treatment of a drug overdose involves supportive treatment, administration of an appropriate antidote (if any), and initiation of measures to decrease absorption and/or increase elimination of the drug. If the respiratory depression is severe, manual or mechanical ventilation may be required.

Respiratory depression and apnea in patients with COPD on supplemental oxygen can be prevented by using relatively low concentrations of oxygen (24-28%). If these patients begin to show signs of worsening respiratory depression, decreasing LOC, or apnea, oxygen supplementation should be halted and the oxygen saturation monitored closely. As the saturation drops, the patient should regain their ventilatory drive. However, one must be ready for immediate airway management if the patient does not begin to breathe and the oxygen saturation continues to fall.

Conclusions

Metabolic or respiratory acidosis can be a sign of a medical emergency requiring immediate attention. The acidosis itself is rarely life threatening, but by following the systematic approach outlined above, the characteristics of the acid-base disturbance can be exploited to guide the clinician to the correct diagnosis. Once the diagnosis is made, treating the underlying condition responsible for the production of the acidosis is the key management strategy.

Acknowledgements

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Law and Ethics in Medicine

The Complaints and Discipline Processes for Physicians: What You Need to Know

Aditya Bharatha, B.Sc. (OT3)

Philip Buckler, B.Sc. (OT3)

(both authors contributed equally to this article)

One of any practicing physician's greatest fears is undoubtedly the patient complaint. Yet, few medical students gain an understanding of the complaints and discipline processes during their training. Such a lack of understanding can only exacerbate what can prove to be one of the most stressful events in a physician's career. Indeed, in a recent survey, over 70% of physicians reported "significant" levels of stress during the complaint process and, for the majority, the stress lingered even after the complaint was resolved.¹

Most doctors are involved in thousands of patient interactions each year, the overwhelming majority of which do not result in a complaint. Nevertheless, complaints are extremely common. Between October 1, 1999 and September 30, 2000, the College of Physicians and Surgeons of Ontario (hereafter referred to as the CPSO, or the "College") fielded 5033 calls about prospective complaints (a near 11% increase over the previous year). Of these, 1372 led to investigations by the College (a 12.3% increase).² This implies that approximately 1 in 20 Ontario physicians is the subject of a College investigation each year.

The Complaint to the College

Under the Regulated Health Professions Act (1991), the CPSO is the governing body entrusted with the responsibility of self-regulating the medical profession in Ontario, through maintaining standards of licensing, practice, ethics and competency.³ Funded through physician membership dues, its role is "guiding the profession and protecting the public".⁴ In order to achieve this goal, both physician and lay public members serve on its various committees.

A complaint regarding a physician typically begins with the concerned party telephoning the CPSO. The complainant is usually a patient, but may also be a family member, or another interested party. The College can also launch its own "Registrar's Investigations", based on information provided by hospital departments or the Coroner's Office. For a formal investigation to proceed, the College must receive a permanent record of the

complaint (such as a letter or an audio-tape). Approximately 70% of calls are handled by intake staff and resolved without such an investigation. For the remainder, the Complaints Committee will assign an Investigator from the CPSO's *Investigations & Resolutions* department to the case. At the direction of the committee, the Investigator may clarify concerns with the complainant and will solicit a response from the physician. The complainant and respondent physician do not meet with the committee; all communication flows through the Investigator. If possible and appropriate, the Investigator will attempt to resolve the matter at this stage by clarifying misunderstandings and facilitating communication between the physician and the complainant. This approach succeeds in resolving 50% of cases.²

In the remaining 50% of investigations, further action by the Complaints Committee is required. The full Complaints Committee is comprised of six physicians and three members of the public. A subset of the Committee, including at least one member of the public, meets to discuss each case. This panel may decide on various courses of action, which are summarized in Figure 1. In the majority of cases, they deem the physician's conduct or care provided to have been appropriate. Uncommonly, they may also deem the complaint frivolous, vexatious, made in bad faith, or an abuse of process. For billing matters, the Complaints Committee may refer the matter to the Ontario Health Insurance Plan (OHIP); for incapacity proceedings (rare), it may refer to the Executive Committee. Alternatively, some mutually acceptable resolution may be negotiated during the proceedings. In this "alternative dispute resolution" process, the physician agrees to undergo a practice assessment, perform certain tasks, and/or make practice changes in order to prevent the Complaints Committee from taking further action.⁵

If the Committee believes that the physician's conduct was not actionable but that the physician would benefit from advice or direction, it may choose to remind, counsel, or caution the doc-

Outcome of Complaints Committee Investigations



Figure 1. Modified from (CCANNREP)

tor in writing. In more serious cases, the physician may be summoned to the CPSO for a "caution-in-person." Prior to such a caution, the physician is frequently expected to have made practice changes, conducted a literature review, or taken other such steps. This is the Committee's way of communicating a strong need for immediate improvement to a doctor thought to be capable of such change.²

In more serious cases involving consistently inadequate patient care, but in which the physician is still felt to be remediable, the Complaints Committee is most likely to refer the matter to the Quality Assurance Committee (QAC). The QAC is able to conduct a more in-depth review of the physician's practice, for example through a peer-review, and may then direct the physician to complete additional remedial work.

In the most serious matters (2.3% of cases), in which "the physician appears to have demonstrated a deliberate disregard for patient welfare, incompetence that does not appear to be capable of remediation, ungovernability [*i.e.*, a disregard for the authority of the CPSO] or otherwise reprehensible conduct", the Complaints Committee will refer the matter to the Discipline Committee.^{2,6}

The Complaints Committee issues written decisions along with their rationale to the complainant and respondent. These decisions can be appealed by either the complainant or the doctor to the Health Professions and Appeal Review Board, which handles appeals from all of the self-regulated health professions. Approximately 20% of Complaints Committee decisions are appealed in this manner. This is the only way to appeal the decision itself; appeals to the courts may be made only on the grounds that the decision was founded on a procedural error.

The Discipline Committee, like the Complaints Committee, is made up of both physician and public members of the CPSO's governing council. Legislation requires at least one physician and two public members to constitute a quorum, however, the CPSO always endeavors to add at least two additional physician members to create a panel of five.⁷ Unlike the Complaints Committee, the Discipline Committee functions as a semi-judiciary body that conducts formal hearings. Hearings are open to the public, except by special order. Present at a hearing are (1) the panel, represented by a chair who acts as spokesperson, (2) an independent lawyer who acts as legal advisor to the

panel, (3) a lawyer retained by the College who functions as the prosecutor, (4) the physician, (5) his/her counsel, and (6) various witnesses, including expert witnesses. During this stage of the process, the prosecutor represents the CPSO rather than the complainant; the complainant is now a witness for the CPSO. The hearing proceeds very much like a trial: charges are outlined, the doctor enters a plea, the prosecution and the defense present their cases, and witnesses testify and may be cross-examined. Medical records are frequently called into evidence, highlighting the importance of documentation.⁸

There are a number of possible outcomes of a Discipline Committee hearing. Similar to a plea bargain, counsel for the College may negotiate a settlement with the physician and his/her counsel. If this does not occur, the panel considers all of the evidence and makes a finding, usually by consensus. This decision is conveyed in writing to the complainant and the doctor. If the physician is found guilty, the parties return to the CPSO for a hearing to establish the appropriate penalty. Penalties may include fines, recorded reprimands, partial or complete license suspensions, revocation of licensure, or an order that the physician undertake remedial work. Both the physician and, rarely, the CPSO prosecutor, can appeal a Discipline Committee decision to the courts.

The Courts

Independent of CPSO proceedings, a complainant or other party who claims to have suffered damage as a result of physician malpractice may launch a civil lawsuit against the doctor. In these cases, the damages are strictly monetary and are paid to the plaintiff. In contrast, fines levied by the College are paid to the Ministry of Health. In 1999, there were 1354 legal actions initiated against physician members of the Canadian Medical Protective Association (Canada's largest physician defense organization, representing virtually all practicing physicians – see below). Of these, 63% were dismissed, 28% were settled out-of-court, 7% resulted in a judgment for the physician and 2% resulted in a judgment for the plaintiff. Out-of-court settlements are reached through negotiations between the physician and the plaintiff. Court awards may reflect both actual damages, such as loss of income or the cost of care, and punitive damages, such as pain and suffering. In 1999, the average amount of a settlement in Canada was approximately \$15,000 and the average court award totaled approximately \$600,000.⁹

In very rare cases, criminal charges arising from patient care may be brought against a physician. In such cases, the Crown Prosecutor initiates charges and a criminal intent must be proven. Court findings, criminal or civil, may be used to support College decisions, but the reverse is not usually true.

Representing the Physician

Due to the significant liability incurred through the practice of medicine, it is essential that physicians carry some form of malpractice coverage. Although Canadian physicians may purchase commercial malpractice insurance, almost every practicing physician in Canada chooses to join the Canadian Medical Protective Association (CMPA). The CMPA is a not-for-profit medical mutual defense organization, founded in 1901 by a group of Canadian doctors and incorporated by an Act of Parliament in 1913. The current membership is in excess of 58,000. Each member pays annual dues based on his/her spe-

cialty and region of Canada, reflecting differences in the average cost of claims. There is significant variation among regions and specialties. Rates in Ontario are the highest in the country; and the specialties with the highest dues are obstetrics, neurosurgery and orthopedic surgery.⁹ Membership dues are put into a reserve fund that provides for physician assistance and indemnification.

The CMPA provides several services to its physician members, including:

- Advice and counseling about how to deal with a potential complaint or a lawyer's letter.
- Advice and legal representation in dealing with or preparing documents for Coroner's Inquests/Inquiries and the proceedings of Complaints, Discipline and Fitness to Practice Committees of Licensing Authorities (i.e., CPSO). Legal representation is provided by lawyers specializing in medico-legal practice and approved by the CMPA.
- Advice and legal representation in the defense of a lawsuit arising from professional work, including payment of legal expenses and any consequent settlements or court awards.
- Advice and legal representation in dealing with hospital matters such as loss of staff appointment or privileges.
- Advice and legal representation regarding billing issues and a host of other miscellaneous enquiries.
- Serving as a policy advocate. Recently the CMPA has argued in favor of structured settlements rather than lump-sum payments to reduce total costs while providing steady income to harmed patients.

Commentary

In this section, we discuss the roles of the CPSO and CMPA, based on interviews with a representative of each organization.

Under the current system of self-regulation, the regulatory body (CPSO) assumes the roles of judge and jury. It has been argued that such an arrangement is not ideal because it may compromise the objectivity of the regulatory body. However, members of most professions view self-regulation as highly desirable because it allows the membership to direct policy and maintain standards, rather than placing these responsibilities in the hands of others. Dr. Indu Gambhir, Assistant Secretary-Treasurer of the CMPA, agrees that all self-regulated professions have this combination of roles and most professions want to be self-regulated. Dr. Michael Szul, Medical Advisor and Associate Registrar in the Investigations & Resolutions Department of the CPSO, asserts that the College believes it can remain objective. He does acknowledge that this issue is often raised, and is periodically reviewed. In response to patient concerns, last year the Ministry of Health commissioned an external review of the complaints and discipline process at the College. The final report is pending.⁵

Accessibility is another issue of public concern. The CPSO must ensure accessibility while maintaining an efficient process that is not subject to abuse. To ensure accessibility, the CPSO is willing to accept complaints in any permanent form, there is no fee, and complainants need not retain a lawyer. In the interest of maintaining equal access, College staff and the Complaints Committee strive to ensure that all complaints are handled with diligence, regardless of the source. Dr. Szul states that it's a good system because it doesn't disadvantage those with limited resources.⁵

Although a very small minority of cases are found to be truly frivolous, vexatious or an abuse of process, Dr. Szul reminds us that, "It takes a lot for an individual to be angry enough to lodge a complaint. For that to happen, it has to be a particularly strong or moving experience for the individual". For this reason, it is imperative that complaints be taken very seriously and complainants treated with the utmost respect. Dr. Szul says that even improbable or impossible complaints are dealt with in a very sensitive way and will not be labeled as frivolous, and goes on to note that most physicians will respond to such complaints in a very respectful manner.

The CPSO is also mindful of the toll that the complaints process can exact on physicians. Dr. Szul acknowledges that the system can be "an annoyance to the doctor". Dr. Pat Ceresia, CMPA medical secretary, confirms this observation: "The emotional spectrum spans anger and outrage to self-recrimination and despair".¹¹ In a recent survey of CMPA members immediately following the resolution of a complaint, Dr. Gambhir reports that over 50% were disillusioned with the process, over 40% developed a distrust of patients, over 20% experienced a loss of caring and compassion, and over 20% considered a change in profession. Comments elicited "reflect the anger, frustration and anxiety that result from [physicians'] sense of a loss of control". One physician reported feeling vulnerable to complaints even when there was no wrongdoing.¹ Moreover, the length of time necessary to resolve the complaint can prolong the suffering of both the physician and the complainant. The CPSO strives to settle cases within one year, and achieved an 86% success rate last year,² but Dr. Szul admits that this is a major area for improvement.

On the positive side, in Dr. Gambhir's survey, over 40% of respondents gained an appreciation of the value of doctor-patient communication, and a significant proportion reported increased appreciation of good clinical care and co-worker communication. Over 20% changed their record-keeping approach and approximately 15% felt that they became better physicians. The issue of adequate medical record keeping was a recurring theme, as one respondent noted: "Defending myself . . . depends greatly on documentation of all patient encounters and details".¹ Such improvements in clinical practice may directly improve patient care; moreover, the fact that physicians are held accountable for the care they provide serves to enhance public confidence in the profession.

A common sentiment expressed by Drs. Szul and Gambhir was the need for enhanced complaint prevention by physicians. Prevention can take a number of forms, including enhanced communication, awareness of boundary issues, improved record-keeping, and continuing medical education. Both the CPSO and the CMPA provide documents and courses to assist physicians in preventing complaints. The CPSO focuses on ensuring that physicians maintain the appropriate standard of care, while the CMPA emphasizes risk-identification and strategies to prevent medico-legal problems. The CMPA even offers a course for medical students. In addition, Dr. Szul feels that the CPSO's goal of universal peer review will facilitate the identification of practice weaknesses before they generate complaints. He argues that all of these measures will "reduce hassles, improve [the physician's] enjoyment of medical practice and improve his/her effectiveness as a physician".

Conclusion

Dissatisfaction with physician care can result in a complaint to the CPSO and/or a civil lawsuit, while allegations of criminal conduct related to the provision of care are resolved through a criminal trial. In all of these matters, physician members can seek assistance from the CMPA. While it is tempting for physicians to regard the CPSO complaints system as an inconvenience, a system for dealing with concerns regarding the provision of health care is necessary in order to protect the public interest and to maintain the reputation of the profession in the eyes of the public. Self-regulation is highly desirable, but with it comes the responsibility of policing the profession. The CPSO complaints process attempts to balance accessibility and fairness with the need to limit the burden of unnecessary and time-consuming complaints investigations. Future efforts to expedite the complaints process and increase preventive measures can only serve to improve the effectiveness of the system.

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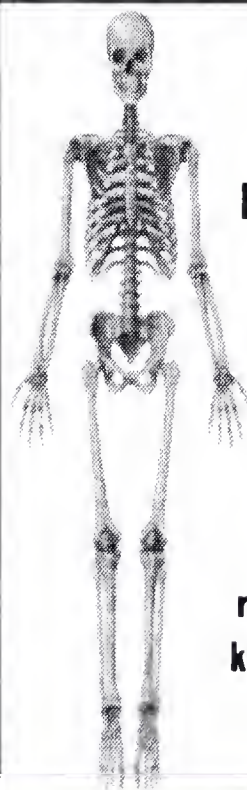
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Evidence-Based Medicine

The Value of Mammography in Screening for Breast Cancer

Ann M. Stewart, M.Sc. (OT4)

This article, the seventh in the *UTMJ* series on evidence-based medicine (EBM), reviews the continuing debate on the use of mammography in breast cancer screening. The debate has been rekindled by the recent publication of new data from the Canadian National Breast Cancer Screening Study (CNBSS), a randomized controlled trial to assess the contribution of mammography, over and above clinical examination, to the reduction of breast cancer mortality. The goals of EBM are to encourage physicians to ask questions and seek answers from the best available evidence in the literature, and to integrate this evidence with their clinical expertise and their patients' values.

Last September, Miller *et al.* published the most recent results of the Canadian National Breast Screening Study (CNBSS).¹ The results were both poorly understood and widely reported in the media. They confirmed previous findings which indicated that although screening with mammography detects more and smaller cancers than screening with clinical breast examination (CBE) alone, this early detection did not reduce overall mortality from breast cancer. This study is the most recent chapter in a debate that has spanned decades, often pitting cancer researchers against radiologists and the mammography industry.

Hypothetical Case Scenario

Mrs. Q, a 55-year-old Caucasian woman presents for the first time at your clinic. She is post-menopausal and has been taking hormone replacement therapy for six years. A close friend of hers has recently been diagnosed with breast cancer and Mrs. Q is worried about her own chances of developing it as well. She asks you to help her "get this worry off my mind." You suggest that she is eligible for mammography, but Mrs. Q refuses, saying she has heard mammography is uncomfortable and sometimes gives incorrect results. How do you proceed?

Discussion

The September 2000 publication from the CNBSS reported the results of a randomized controlled trial involving 39,405 Canadian women aged 50-59. Women were randomly assigned to two groups: one group was screened with mammography and thorough CBE, the other with CBE alone. Screening was performed annually for 3 or 4 years, depending on the date when an individual entered the study. The women were then followed to determine incidence and mortality from breast cancer and results were documented for 13 years after entry into the study. The results indicated that although mammography detects more cancers and cancers of a smaller size, there was no difference between the two groups in the rate of breast cancer deaths for up to 13 years following screening.

These are the latest in a series of results from the CNBSS that have generated a great deal of controversy. There is little doubt that

screening for breast cancer reduces the number of women who will die from the disease, as was first demonstrated in the 1960s in a study done by the Health Insurance Plan of Greater New York.² Identification of the cancer in its early stages can result in earlier initiation of therapy, less invasive surgery and a greater rate of survival. Although there have been significant differences in opinion over the appropriate age to begin screening,^{3,4} much of the literature describes mammography as the gold standard of early disease detection.^{5,6} Indeed, many clinicians assume that because mammography allows the detection of a greater number and smaller sized tumours than palpation, it must be a superior method which leads to increased survival.

Given the widespread acceptance of this assumption, one might wonder why physicians continue to perform CBE at all. There are, however, several benefits to CBE. First, many women simply choose not to have mammography. They find it uncomfortable and fear its false alarms and assurances. Indeed, given the significant numbers of false positive and false negative results, it is important to complement mammography with CBE. Miller *et al.* suggest CBE as an alternative to mammography, a separate technique with its own merits. In particular, they recommend CBE for women aged 50-59 who decline screening mammograms. Physicians can be confident that if their examinations are thorough, they can be as useful to the patient in reducing the risk of mortality from breast cancer as mammography. Several studies have shown that the sensitivity of CBE alone can be as high as 64% for women aged 50-59, and the specificity approximately 95%.⁷ By contrast, the sensitivity and specificity of screening mammography have been reported as 72% and 97%, respectively.⁸

It should be noted that an effective CBE includes more than searching for palpable masses, obvious nipple discharge, scaling of the nipple, peau d'orange, or skin retraction and dimpling. A thorough CBE should take up to 10 minutes, and involve careful visual inspection of the breasts with the woman in upright and supine positions, viewing the breasts from several angles, and looking for asymmetries in size and variations in the shape of the breasts, retrac-

lumps and ulcerations of the breast surfaces, and other anomalies. A methodical palpation technique must be used to detect thickening or lumpiness of breast tissue, as well as cystic lesions.¹

Bobo *et al.* found that CBE was sensitive enough to detect many cancers in community-based screening programs, and observed that, within their cohort, up to 16% of cancers found may have been missed if only mammography had been used.⁹ Mittra *et al.* further suggest that CBE may be the ideal screening tool, since it is simpler and less expensive than mammography while appearing to be “as effective.”¹⁰

In the most recently published report, Miller *et al.* state that their findings do not negate the value of screening with mammography as compared with no screening at all.¹ The researchers believe that screening mammography should still be performed since it may be easier for women to access high-quality mammography than high-quality CBE, particularly since not all physicians are trained in the techniques described above. Also, there is some evidence that mammography and CBE are complementary in their detection of tumours; it may be wise to use both techniques, especially if there is any doubt about the presence of a lump.^{7,9}

Critics of the CNBSS had voiced complaints about the quality of the study, even before publication of its results, citing problems with the randomization protocol and supposedly poor technical quality of the mammography.¹¹ The issue of improper randomization was investigated at the request of the National Cancer Institute of Canada, and no evidence was found that the process had been subverted.¹²

A recent article by Gotzsche and Olsen also validated the quality of the CNBSS radiography, suggesting that the Canadian study found tumours that were smaller on average than those found in Swedish trials.¹³ The Gotzsche and Olsen paper suggests that the Canadian trials have been the subject of much criticism because of the nature of their results. One must recall that mammography is a multi-billion dollar industry and many people may be opposed to the idea that CBE may be a preferred alternative to screening mammography.

Conclusion

To resolve the case scenario above, the evidence shows that you can adequately allay Mrs. Q's fears without resorting to mammography by performing a thorough CBE. However, you must advise Mrs. Q that if anything unusual is found during the clinical breast examination, follow-up with diagnostic mammography is strongly recommended.

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Editorial Addendum

In February 2001, the Canadian Task Force on Preventive Health Care (CTFPHC), published updated recommendations for the use of mammography as a screening tool for breast cancer in women aged 40-49 years.¹⁴ The CTFPHC review found that there is currently insufficient evidence to include or exclude screening mammography from the periodic health exam of women in this age group (grade C recommendation). In contrast, “there is good evidence for screening women aged 50-69 years by CBE and mammography,” every 1-2 years (grade A recommendation). For other recommendations regarding breast cancer screening, please see the CTFPHC website (<http://www.ctfphc.org>).

The use of CBE versus mammography as screening tools remains a highly controversial issue, as described in this article. There have been no published randomized controlled trials to clearly show the survival benefits of one technique over the other, and numerous cohort studies, both prospective and retrospective, have fueled much debate with conflicting data and data analysis. For example, Bobo *et al.*⁹ emphasized their finding that 16% of cancers found in women with abnormal CBE findings may have been missed by screening mammography alone. However, raw data given in the same article indicate that, in the population studied, 38.4% of cancers found in women with abnormal mammograms may have been missed by CBE alone. In the wake of such uncertainty, all current recommendations by the CTFPHC¹⁵ as well as the U.S. National Institutes of Health¹⁶ concerning breast cancer screening include *both* CBE and mammography as complementary techniques, with specific guidelines for different age groups.

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Forum

Access to Medicines - The Global Debate Over "Free Trade"

Tanya L. Zakrison, M.H.Sc., (OT3)

Paul A. Hamel, Ph.D.*

Forum

This section, new to the *UTMJ*, presents a current issue facing the medical community. Following an objective presentation of the issues, individuals involved in the course and resolution of the problem are invited to voice their perspectives. The ultimate aim is to stimulate discussion.

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The new millennium has ushered in an era of what is known as globalisation.¹ This system is purported to be based on the principle of "free trade". The intention is to stimulate economic growth that, ultimately, will translate into higher standards of living for the world's people. However, opponents argue that globalisation is the projection of the West's economic and military power. This perspective sees free trade as designed to perpetuate the wealth of affluent nations, by protecting access to markets and resources that North Americans and Europeans disproportionately consume. Central to this global debate is a series of agreements, one known as the Trade-Related Aspects of Intellectual Property Rights (TRIPS). Among many other aspects, TRIPS attempts to regulate the use of inventions through patent protection rules. The debate over access to essential medicines² primarily focuses on this agreement.

In 1996, 17.3 million people (>90% in the economically disadvantaged world) died of infectious diseases such as malaria, tuberculosis, leishmaniasis, onchocerciasis and AIDS. As citizens of prospering nations, we often dismiss these deaths as the unfortunate result of poverty, corruption or mere economic incompetence, that prevents persons in many countries from affording life-saving medicines that already exist and are on the market. But if access to contraceptives or vaccines has already been established as a priority by the United Nations (UN), why are these life-saving drugs not similarly available? There are several sides to the dispute surrounding access to life-saving medicines and the broader ramifications for all parties involved.

Multinational pharmaceutical corporations defend the view that it is risky and costly to invest millions of dollars and energy into the research and development (R & D) that is needed in order to produce life-saving medications. Thus, it is argued that the

chemical entity or process to produce it needs to be protected for the exclusive use of the inventor in order to profit from their invention (i.e. patent protection). Patent protection usually approaches 20 years for drugs, and guarantees that all aspects of production, marketing, pricing and use of the drug/invention are under the control of the patent holder. Opponents to pharmaceutical companies equate this to granting a legal monopoly. Globally, patent rights and protection fall under intellectual property rights and have been governed by TRIPS under the World Trade Organization³ (WTO) since 1994. The pharmaceutical industry argues that the current rules setting the length of time that a patent is enforced allows them to recoup the costs of R & D. This, in turn, generates significant return on investment for their shareholders thereby stimulating further risk-laden R & D. Without all countries abiding by the same standard of patent protection to respect intellectual property rights, pharmaceutical corporations claim that the loss of profits would be detrimental. It would destroy their incentive to continue investment in the development of novel formulations urgently needed to combat new and old infectious agents. These same companies deflect responsibility for guaranteed access to medicines in poor countries since it is not their mandate to deal with "endemic problems of poverty, ignorance, neglect and corruption [which] undercut meager health services, keep populations isolated, perpetuate risky behavior and render drugs alone ineffective."⁴ In fact, through philanthropic gestures, many pharmaceutical companies argue that they already donate certain desperately-needed drugs to the sick the world over. International and UN pressure led to the recent announcement in May 2000 by five of the largest pharmaceutical companies that they will lower the price of their AIDS medications by up to 85% for people living in poor countries.⁵ Thus, the corporations argue that internationally-applied and respected patent protection with TRIPS is the key to innovation, research and accessibility and that the pharmaceutical industry is ready to be a partner in global public health.

Contrary to the pharmaceutical industry's claim, many governments and non-governmental organizations (NGO's) around

*Department of Laboratory Medicine and Pathobiology, University of Toronto

It would maintain that patent protection under TRIPS denies patients the essential drugs needed to survive the infectious scourges endemic in their countries. Médecins Sans Frontières (MSF) is one such NGO that in 1999 launched a campaign for "Access to Essential Medicines". "The reality is that many of the world's killer diseases are treatable, but the drugs are either too costly, no longer produced or lacking in quality or effectiveness. Furthermore, research for diseases that affect people in poor countries has ground to a virtual halt. Multinational companies will always aim for maximum profits by marketing a new obesity drug in Europe, North America and Japan rather than pioneering a novel malaria treatment" stated MSF (www.accessmed.msf.org).

The pillars of the MSF campaign rest on three main issues: i) exploitation of health exceptions built into trade agreements, ii) overcoming barriers to access of essential medicines and iii) stimulation of research and development for neglected diseases. These measures proposed by MSF do not challenge the principal foundations of TRIPS or the economic system organized under the WTO. In fact, MSF-advocated and TRIPS-consistent measures are frequently enjoyed by Western countries in order to protect their own domestic industries. These include such measures as compulsory licensing,⁶ parallel imports⁷ and steps to accelerate the introduction of generic drugs on the domestic market (bolar provisions). MSF has also demonstrated in their publication *"Hidden Price Tags: Disease-Specific Drug Donations: Costs and Alternatives"*⁸ that the much-touted donations of essential medicines by pharmaceutical companies are, in fact, mostly deleterious to health infrastructure, local drug industry, patient health, and incur excess cost borne by the public in donor countries. MSF proposes stimulation of local generic drug industries as an important goal for sustainable access to essential medicines. The Access to Essential Medicines campaign attempts to hold to task the benefits of liberalized trade rules promised and promoted by the pharmaceutical industry under the WTO.

In contrast to the positions of the pharmaceutical industry and MSF, other groups and individuals contend that it is not WTO legislation that is the barrier to essential medicines, but rather the WTO-regulated system itself. With the predominant influence of the United States at its helm, the rules of the WTO, such as TRIPS, maintain large segments of the world's populations in conditions of ill-health and poverty without access to essential medicines in their "race to the bottom".⁹ It has been pointed out that agreements such as TRIPS are so obviously detrimental to public health that embedded within these agreements are safeguards limiting foreseen damages inflicted by its own legislation. The UN maintains that patent protection under TRIPS undermines food security and public health in developing nations by making it much more costly to procure seeds for crops or to make medicines more accessible to the public.¹⁰ Furthermore, despite promoting adherence to TRIPS, supereconomies (namely the US) use a variety of economic tactics to prevent countries from invoking legal TRIPS safeguards. India, for example, has fiercely defended its legislated protection of agriculture and medicines by barring these from their Patent Act of 1970. They have been pressured, however, to pass legislation which contradicts and supersedes their national regulations¹¹ thus supporting the notion that economic rules enforced by powerful countries in the WTO take precedence

over local domestic, social and cultural laws. There is a litany of examples (e.g. Thailand, South Africa, Ukraine, Israel, and Canada) that demonstrate how nations applying the TRIPS safeguards have engendered the economic fury of powerful trading partners in the name of protecting markets and "national interests".

The opponents of TRIPS also point to the "misuse" of the Agreement when it is used by companies to acquire and patent indigenous knowledge and resources. Certain indigenous medicines that have been in use for thousands of years have become labeled with a US patent office number only to be sold back at a high price to those initially responsible for cultivating the knowledge. This "biopiracy" which is an unbridled transfer of technology from poor countries to the rich, is also included under the umbrella of intellectual property rights where rich countries expand their wealth by appropriating the knowledge of indigenous peoples and protecting it under patent laws.¹² With UN Secretary General Kofi Annan creating initiatives such as the new Global Compact that forge partnerships between UN agencies dealing with the environment (UNEP), labour (ILO), human rights (UNHCHR) and the private sector, the preservation of democracy becomes a pressing issue for all of our collective futures (www.unglobalcompact.org).

A) THE PHARMACEUTICAL VIEW **– The International Federation of Pharmaceutical Manufacturers**

Harvey Bale, director general of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) presented a position paper on the effects of Globalisation and Access to Medicines and Vaccines¹³ representing the point of view of 55 national industry associations. Mr. Bale spoke about the importance of innovation leading to new medicines as crucial for meeting public health challenges in developed and developing countries. "By permanently bringing to the market new drugs for unmet medical needs, the research-based pharmaceutical industry contributes to enhancing public health throughout the world, including countries where tropical diseases are a special problem." Globalisation will lead to more research being done in the pharmaceutical industry on a global basis than is being done today, namely as the result of recent international trade agreements, particularly WTO's agreement on TRIPS. Bale points to the local companies in developing countries, that are responding to the "new order" by increasing their efforts to find new medicines. He states that according to local industry association reports, Indian companies are responsible for most of the increase in pharmaceutical patent filings last year. As a result, Indian society and the world will be much better off over the longer term because TRIPS is encouraging local companies to shift from copying with generics, to invention. With respect to developed nations, experience from Spain, Italy, Japan and Canada, all of whom have refined and upgraded their pharmaceutical patent laws, shows that local producers do not suffer greatly when increases occur in local research and development.

When explaining why the pharmaceutical industry incurs such high costs of R & D, Bale explains that it is the commercial industry that undertakes the risks of doing multi-year tests on the effective dose, proper indications and safety profiles of new chemical and biological compounds. The failure rate is high with only one medicine receiving marketing approval out of the

thousands of compounds screened for therapeutic benefit and only one medicine out of five entering clinical trials being approved for patient use. Furthermore, the industry claims it takes 10 years on average from discovery to delivery to the patient. Strong intellectual property protection throughout is essential to recoup these costs. In fact, the TRIPS agreement goes far to assure that new medicines will be forthcoming to patients in both developed and developing countries. Stronger worldwide patent, trademark and trade secret protection promise to increase access to new therapies for currently incurable diseases, maintains Mr. Bale.

When faced with the dilemma of access to medicines, and pondering whether international trade agreements will have an adverse effect on access to essential medicines, Mr. Bale responds that this is not a one-dimensional issue related to price alone. Many other factors are responsible for preventing access. Again, pointing to unreferenced research from India, Bale explains that poor management, misuse of self-medication, low level of public expenditure on health care, lack of basic infrastructure, inadequately trained personnel, and the lack of adequate health care infrastructure are all responsible for affecting access to medicines. He wonders exactly how far giving drugs away for free would go to solve the access problem? He answers his own rhetorical question by stating "probably not very far."

Concerning the impact of adoption of new international agreements on local pharmaceutical prices, Mr. Bale feels that "no generalization can ever apply to *every* specific situation". He states that this lack of effect on price is due to patent laws not acting retroactively. Thus any product legally on the market at the time that a patent law comes into force is unaffected, allowing patented and generic drugs to exist side by side in the market. He argues that other factors usually have a greater impact on prices: the market structure, existence of distribution bottlenecks and artificial distribution margins, regulatory and tax conditions, inflation, exchange rates and the pattern of drug consumption.

Access to essential medicines is occasionally facilitated by drug companies providing donations to specific health institutions in certain countries. Examples include recent corporate initiatives taken together with UNAIDS to tackle onchocerciasis, filariasis and trachoma. In 1999, Merck & Company, Johnson & Johnson and Pfizer each reported (tax deductible) product donations of over US \$100-million to developing nations unable to afford the price of patent-protected drugs.¹⁴

In concluding his speech, Harvey Bale asked the question of whether commercial companies are partners in public health. If so, he stated it needs to be recognized that the companies' contributions through discovery and invention can only be fostered by avoiding threats to patent and trademark protection. What is needed is a long-term global partnership between the WHO (World Health Organization), industry, national governments, international funding agencies and the WTO. All can play complementary roles in doing research and development work, strictly enforcing patent and other intellectual property laws, providing adequate funding in countries which lack adequate resources and improving access through the improvement of local infrastructure.

B) THE HUMANITARIAN VIEW – Médecins Sans Frontières

Médecins Sans Frontières has been on the forefront of a growing number of organizations and NGO's that have repeatedly challenged the issue of limiting access to essential medicines in the interest of abiding by international market forces. This came as a result of the collection of experiences of MSF field workers. Recent high profile examples include the outraged MSF staff in Nairobi who witnessed AIDS patients with cryptococcal meningitis being told to go home and die, as the price of the only effective treatment, a patent protected drug, was beyond their means. More specifically, the "*Access to Essential Medicines*" campaign pillars can be broken down in the following manner:

i) *Health exceptions to trade agreements:*

Here MSF directly addresses the regulations introduced by the TRIPS Agreement of the World Trade Organization (WTO) allowing pharmaceutical corporations complete global patent protection as of the year 2006. The implementation of the TRIPS agreement will have a negative effect on the developing world's capacity to manufacture affordable generic drugs and will therefore lead to an increase in drug prices. This emerging global trade system is treating medicines as it would textiles, compact discs or t-shirts. By allowing patenting of medicines, a market monopoly is conferred to pharmaceutical companies that charge the same high price to buyers whether they live in New York City or in Tegucigalpa. MSF proposes to increase the local production of good quality drugs as well as the importation of less expensive essential medicines. This strategy can be done legally through the WTO loopholes afforded to countries in the interest of public health and in order to prevent or resolve national medical emergencies or crises. Countries should also have the ability to produce their own generic drugs as a more sustainable solution, aided by a transfer of technology from the economically advantaged nations. MSF suggests that the WHO should step up its efforts in defending public health interests against the increasing dominance of commercial ones. MSF also believes that the G8 (eight most economically powerful nations) should issue an unequivocal statement that its member countries will not pursue retribution against countries that implement TRIPS-consistent measures (licensing, imports and generics) in response to health needs.

ii) *Overcoming access barriers:*

This second pillar of the Access to Essential Medicines campaign is based on the premise that many people in the world are dying of preventable and communicable diseases simply because they cannot afford the price of the medication. In other cases, pharmaceutical corporations have stopped manufacturing life-saving treatments when the drug is no longer profitable. For example, cflornithine for sleeping sickness (Human African trypanosomiasis) was discovered in 1985, sold at an extremely high price, then had its manufacturing discontinued due to a lack of commercial interest.¹⁵ The emphasis now is for the pharmaceutical industry to produce drugs that can enhance the lifestyles of the rich, e.g. treatments for baldness or impotence. To overcome this problem, MSF strategies include conducting global price analyses of selected essential drugs deemed too expensive (e.g. fluconazole, ciprofloxacin, azithromycin) in order to negotiate better prices and demonstrate price differences from different manufacturers. For example, the June 2000 MSF "*HIV/AIDS Medicines Pricing*" report

and tremendous variation in brand drug prices in different countries. The single most important determinant of these differences is market monopolization.

The MSF report also demonstrates that the presence of generic drugs on a market leads to dramatic price reductions for all drugs (patented or generic). Before fluconazole was produced as a generic in Thailand in 1998, Pfizer sold it for US\$7 per 200 mg capsule. With the introduction of generic equivalents by three Thai companies, Pfizer dropped the price to US\$3.60 even though the generic drug was still much cheaper (US\$0.60 by Biolab). Thanks to the competition afforded by generics, cryptococcal meningitis is now a treatable disease in Thailand. Anti-retroviral medication prices have also dropped due to generic competition¹⁶ and now cost an average of 90% less than US prices in some "developing" countries. This last example further demonstrates that even price reductions of 85% promised by 5 pharmaceutical companies and UNAIDS (duty yet to be fulfilled) would still be higher than the prices offered by generic producers. The UNAIDS initiative amounts to a price reduction of only 6.7 times when concerted international procurement efforts on vaccines and oral contraceptives¹⁷ have reduced prices by 33 and 240 times respectively, when selling to disadvantaged nations. One must question whether this offered reduction for anti-retroviral medication is a response of adequate magnitude for the current AIDS pandemic.

Interestingly, MSF also found pharmaceutical donations to be at times more harmful than helpful. Donations were unsustainable as they adhered to the whim of the corporations and were encouraged by the system of tax incentives of the US government. They were also damaging to the local health and pharmaceutical infrastructure, leading to future dependency on the donation in question.

iii) Stimulating research and development for neglected diseases:

The last pillar of MSF's multifaceted campaign is in direct response to the lack of research for communicable diseases. Out of 1,223 new drugs developed between 1975 and 1997, only 13 (1%) were aimed at tropical diseases. Of these 13, only 4 were the direct result of R & D activities of the pharmaceutical industry, the rest stemmed from military research and veterinary use. The reason for the lack of interest is that pharmaceutical companies feel that drugs for tropical diseases are not profitable. At the Okinawa International Conference on Infectious Diseases (Dec., 2000), Dr. Bernard Pécoul of MSF made several recommendations to combat this problem. These included the definition of a need-driven research agenda for new medicines and vaccines that would lead to the development of 10 to 20 new drugs over the next 10 years. Dr. Pécoul suggests that governments should demand that a small percentage of profits in the private sector go towards developing essential medicines for neglected diseases. By negotiating an international treaty, R & D can be ensured for neglected diseases and the affordability of developed drugs or vaccines can be guaranteed.

MSF also finds fault with the over-used argument given by the pharmaceutical industry that the cost of R & D is very large and therefore justifies patent protection to recoup these costs in order to stimulate further R & D. A large amount of the R & D that ends up in a marketable pharmaceutical product is the

result of public financing, as many drug discoveries are made in publicly funded institutions such as universities. MSF found that for five of the six anti-retroviral medications analysed in the HIV/AIDS Medicines Pricing Report, public funding played a significant role in drug discovery and/or clinical research. Even the Pharmaceutical Manufacturers of America (PhRMA) estimates that private industry finances a mere 43% of drug development.¹⁸ The lengthy time for drug approval is another factor commonly cited by pharmaceutical companies for justifying high prices. This excuse is difficult to support as recently developed anti-retrovirals are some of the most expensive drugs on the market and yet these drugs enjoyed the shortest time-to-approval of any class of drugs, with a mean time to market half the industry average.¹⁹ It would seem that many of Mr. Bale's corporate arguments become deflated after facing the evidence provided by MSF research. MSF maintains that by applying for compulsory licensing, parallel importing or calling for an increase in R & D into tropical diseases, patients will be able to increase their access to essential medicines within the framework of the WTO.

C) THE HUMAN RIGHTS VIEW

To date, the outlook in the quest for essential medicines for the majority of the world's people looks grim. Of all the countries in the world necessitating urgent access to medicines, especially to treat HIV, only one (Senegal) has negotiated a price reduction for anti-retrovirals through UNAIDS' five company Accelerated Access Program. This will benefit approximately 900 Senegalese who are HIV positive, a number that represents less than 0.0035% of the 26 million people who will die a premature death from untreated AIDS in Sub-Saharan Africa. These numbers are dwarfed still by those millions who die annually from other treatable tropical diseases that have traditionally plagued underprivileged nations. Are TRIPS-compliant safeguards sufficient to overcome the lack of access to essential medicines? Indeed, can the access to these essential drugs ever be expected to become remotely sufficient under TRIPS rules given the unambiguous, singular mandate of pharmaceutical companies to maximize profits? A number of examples serve to support the notion that improved access is discouraged or not possible under the current system.

Thailand, with a population of 61 million, has 1 million HIV positive citizens, only a small number of which can afford to buy anti-retroviral medication.²⁰ In 1992, under threat from the US to limit textile imports, the Thai government introduced patent protection on a number of products including medicines. As a safeguard, the Thai government created the Pharmaceutical Patent Review Board (PRB) which had the authority to collect economic data in order to assess the effects of patents on drug availability in Thailand. However, once again under threat by the US Trade Representative Office to increase U.S. import tariffs on Thai wood products and jewelry, the PRB was disbanded in 1998. Nonetheless, during its existence, the PRB managed to induce price reductions for fluconazole by 95% and zidovudine from \$US 324 monthly in 1992 to \$US 87 in 1995, through generic competition. Subsequent attempts at local production of other drugs have not been successful. For example, Bristol-Myers Squibb has exclusive patent rights to didanosine (ddI), and blocked Thai production of this drug. Their success is all the more unreasonable given that the

R & D for ddI was carried out by the publicly funded National Institute of Health; Bristol-Myers Squibb secured a product patent by "developing" the delivery system of ddI. The frustration of this arrangement was articulated by Thai AIDS activist Jon Ungpakorn: "By the time the patents run out, everyone will be dead."²¹ Under continued US pressure, the Thai government also enacted national legislation that impeded the use of compulsory licenses by their country, a law that was even stricter than current TRIPS legislation.

Similarly in South Africa, the international pharmaceutical industry, with assistance from the Clinton administration, fought to reverse the South African Medicines Law that was enacted in 1997 by Nelson Mandela. With the goal of making health care and medicines more accessible to South Africans, this law encouraged the use of generic drugs and instituted parallel imports and compulsory licensing, both legal under Article 31 of TRIPS. However, the US pharmaceutical industry threatened the South African government with a WTO challenge while the US Ambassador to South Africa, James Joseph, urged the South African government to eliminate the parallel import provisions.²² The US Trade Representative went so far as to suspend some of South Africa's Generalized System of Preferences benefits and placed them on the so-called Section 301 "watch list."²³ It was only after tenacious protests by AIDS activists in South Africa and the U.S. (Act-Up) as well as the South African government, that the Clinton administration abandoned all proceedings and retaliatory measures in September of 1999. In early December of 2000, the South African Treatment Action Campaign (TAC) announced another victory with the limited approval for generic fluconazole to be imported from Thailand.

The threat of economic isolation from the West, having membership to the WTO denied, and/or being labelled by the US as a "rogue state" for trying to treat their ill,²⁴ have discouraged aid-dependent countries, like the Ukraine, from attempting to implement legal TRIPS-compliant safeguards. Recently, Glaxo Wellcome successfully blocked access to generic AIDS drugs in Ghana from Cipla Ltd. of India, based on the company's contention that the importation of generics is violating the company's patent protections.²⁵ The African Regional Industrial Property Organization (ARIPO) states, however, that the patents are invalid in Ghana because at the time of issue, Ghana did not grant patent protection to pharmaceuticals. {Nonetheless, Glaxo is concerned about the precedent that will be set when a country considers its sovereign duty to health care to be more important than adhering to thinly-veiled Western market protectionism.}

Of further significant concern is the plundering of countries and ancient societies of their traditional medicines and knowledge by pharmaceutical companies in a form of neo-colonialism. After "re-inventing" and patenting a medicine, it is then resold on the world market under patent protection to the very people from whom the knowledge was first appropriated. While used for its medicinal and pesticidal properties for over 2000 years, the U.S.-based W.R. Grace Company patented the rights to the Neem tree seed for its pesticidal activity (<http://writeshop.org/~vshiva/naturefacts/nccm.htm>). Patent was granted despite the Neem seed not fitting the criteria of a "novel invention" and being, in fact, an "obvious" product to

almost one billion Indians. Plundering of indigenous knowledge knows no bounds as demonstrated in the case of Basmati rice, a patent for which was granted to the Texas-based firm RiceTec. Like essential medicines under the TRIPS Agreement of the WTO, India is required to enforce the American company's patent rights over Indian farmers who have been cultivating Basmati rice for generations.²⁶ Patent-protected "terminator seeds" are genetically engineered varieties that require a purchasable chemical to germinate and are sterile, creating a yearly agricultural dependency of farmers no longer able to use their own seed technology.²⁷ These examples serve to illustrate the growing systematic theft of the resources and knowledge of indigenous peoples, known as "biopiracy".

With water utilities being privatised,²⁸ CO₂ emission blocks being treated as trade-negotiable products²⁹ and human genes belonging to corporate entities,³⁰ what or who will speak out in favour of our inalienable human rights, the common good or equality for all? Recent initiatives at the United Nations suggest that they are undependable in protecting anyone on the planet from the devastating effects of the WTO. Specifically, on July 26th, 2000, Kofi Annan appeared with representatives of some fifty corporations to officially launch "*The Global Compact*". This "program" allies the UN with transnational corporations ostensibly to overcome the UN deficit caused by debtor member nations, principally the US. It is postulated that the one country in the world that voted against a resolution declaring food as a human right (the U.S.),³¹ has monetarily strangled the UN in order for this organization to be "saved" by corporate entities. These are the very corporations responsible for contributing to a system which promotes US economic interests while impoverishing billions of people. Corporations do not have the same mandate or goals as those described in the UN Declaration of Human Rights. Simultaneously, the world is told by the Director-General of the WHO, Dr. Gro Harlem Brundtland that "To develop new drugs we need an innovative pharmaceutical industry, with appropriate incentives for innovation and protection of intellectual property rights". Given the previous experience of impoverished countries attempting to acquire essential medicines, the WHO statement that "From a public health perspective, there are a few key questions: will drug prices increase? Will R & D increase on drugs for priority public health problems? On these questions, let me say, WHO will be watching" suggests that watching by these organizations is all that can be expected. At the 1999 World Health Assembly, the WHO was given a mandate to monitor the public-health consequences of international trade agreements.³² It is inappropriate to ask someone who is perishing of malaria, onchocerciasis, AIDS, heart disease, hunger or torture that they must die in order to become a "consequence" to be counted so that bureaucrats and businessmen behind their closed doors will care.

In 1998, the world celebrated the 50th anniversary of the United Nations' historic Universal Declaration of Human Rights. This declaration, in part, proclaimed that everyone is entitled to a standard of living adequate for health and well-being of the whole family, including food, clothing, housing, medical care, and the right to security in the event of unemployment, sickness, disability, old age, or other circumstances that lead to a lack of livelihood and are beyond the citizen's control (www.un.org/Overview/rights.html). Unlike the rules

the WTO, there exist no mechanisms to enforce these fundamental human rights.

In the context of access to essential drugs, it is clear that countries attempting to invoke the legal WTO TRIPS-compliant safeguards face significant hostility from the pharmaceutical industry and its principal champion, the U.S. government. Fear of economic reprisals and military intervention³³ is a powerful deterrent even at the cost of the health and lives of the citizens of a country. By serious rational criteria and international law, blocking the prevention of the death of millions of people is arguably a matter for international courts responsible for investigating crimes against humanity.

Summary

From a human rights standpoint, there can be no justification for withholding essential medicines from anyone. There are no trade rules, patent laws, or responsibilities to share holders that supersede the lives of people. Thus, any effort to produce important and/or essential drugs in any location around the world should be supported. This paper has presented several points of view with respect to the access of essential medicines. On one hand, the pharmaceutical industry maintains that they have reason to protect intellectual property rights under the TRIPS agreement, and welcome the protection guarded by WTO legislation and enforcement. On the other hand, MSF believes that TRIPS should not be applied to medicines and that poorer countries that cannot afford patent protected drugs should be able to adhere to TRIPS-compliant safeguards allowing them access to generic medicines. The authors maintain that evidence indicates that TRIPS safeguards are disrespected when enacted and that the whole WTO-based system of economic trade is what is detrimental to the health and well-being of humankind.

Addendum

On March 5, 2001, a landmark court case began in Pretoria, South Africa in which 39 multinational drug firms are taking the South African government to court by challenging their Medicines Act (legal under the WTO). This is to prevent the government from purchasing cheaper generic drugs for their 4.5 million South Africans infected with HIV. Five of these leading multinationals have global sales well over three times South Africa's entire national budget (GlaxoSmithKline, Merck and Co., Bristol-Myers Squibb, Roche, and Boehringer Ingelheim). The ramifications of such a disastrous precedent are clear for all countries around the world.

Footnotes and References

1. Globalisation= economic, political, social, cultural and military interdependence. In other words, globalisation, is equivalent to a transformation of society resulting in the negation of territorial frontiers.
2. Essential medicines refers to drugs that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage form. The WHO Model List of essential drugs is intended to be flexible and adaptable to many different situations, exactly which drugs are regarded as essential remains a national responsibility.
3. The World Trade Organisation is the institutional successor to the General Agreement on Tariffs and Trade (GATT). This Organisation has international legal status and henceforth all matters relating to international trade will fall within its jurisdiction. The WTO agreements consist of multilateral agreements that become binding upon Member States when they join the WTO, and plurilateral agreements that are optional.
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Use of the Internet by Canadian Physicians and the Influence of the Internet on the Doctor-Patient Relationship

Steve K. Singh, B.Sc. (OT3)

On an oil rig off the coast of Newfoundland, a nurse stabilizes a critical patient, with numerous fractures and difficulty breathing, by following the instructions of trauma specialists observing in St. John's via digital cameras and a high-speed Internet connection. At the Cape Breton Healthcare Complex in Sydney, Nova Scotia, pediatricians successfully attend to a premature baby with a congenital spinal anomaly by transferring laboratory values and X-ray images over the Internet to expert neonatologists in Halifax. Although these vignettes may sound like science fiction, these remarkable medical feats are possible today as a result of recent advances in communications technology, particularly the Internet.¹ These projects enhance the quality and accessibility of sophisticated medical care, but are, as of yet, limited in their widespread application because of the costs of this technology.

As time is increasingly scarce for many overworked physicians, the Internet's potential to improve the efficiency of health care delivery is very attractive.¹ Today, with the mere click of a mouse or stroke on a keyboard physicians are able to do everything from research online to communicating with patients, and even billing for services.¹⁻³ This article summarizes a survey published in the *Medical Post* on the Internet practices of Canadian physicians.¹⁻⁴ It also provides quotations from Canadian physicians that represent the attitudes expressed about the potential benefits of the internet for practicing physicians.

Since the Internet has only recently begun to find its way into medicine, data on Internet usage is limited. The *Medical Post* recently published the results of its "2000 National Survey of Doctors", which included statistics on the use of the Internet by Canadian physicians, along with testimonials on how they have adapted themselves and their practices to this technology.¹ However, it should be noted that this questionnaire was administered by fax or online at the *Medical Post* website, so it is likely that this survey over-represented physicians that use the Internet regularly.

The *Medical Post* survey reported that the majority of Canadian physicians welcome the expansion of the Internet into modern medicine. Most physicians agree that the Internet has much to offer in terms of reliable information. However, many have reservations about the potential applications of the Internet, and fear that the absence of regulation on the World-Wide Web may lead to the dissemination of

inaccurate information to patients.

In Canada, male doctors (60%) are more likely to use the Internet than female doctors (40%). Fifty-seven percent of Canadian physicians reported online access both at work and at home. Specialists (66%) are more likely than family doctors (46%) to have access to the Internet. Overall, Canadian doctors surveyed reported using the Internet for the following tasks:

1. Gathering information about drugs or medical products	73%
2. Gathering information on treatment protocols	61%
3. Consulting with colleagues	42%
4. Taking continuing medical education (CME) courses	24%
5. Sending e-mails to patients	23%
6. Filing billing information	19%
7. Participating in clinical trials	8%
8. Writing prescriptions online	1%

There was tremendous use of the Internet by physicians to gather information on drugs or medical products, treatment protocols and/or to further medical education. Consulting with colleagues using e-mail was also a widespread practice among Canadian physicians. These were all unanimously cited in the surveys as time-saving and convenient.

While participating in clinical trials using online resources was utilized by only 8% of Canadian physicians surveyed, 34% of those who did not use this service said that they had great interest in applying it to their practices in the near future. Dr. Philip Baer, a Toronto-based rheumatologist, summarized the power of this application when he suggested that e-mailing large bodies of people who belong to an association for a particular disease could be an expedient method to recruit patients and investigators, and as a result, collect outcomes and conduct research more efficiently.

Similarly, online billing is a practice that only 19% of Canadian physicians performed, but of those responding that they had not used this service, 40% listed on their questionnaire that they were "very or extremely interested in such a service" in the future. What had prevented this task from becoming widely used was the issue of data security.

In general, questions about security on the Internet are common concerns of physicians. "I'm not sure that we're at the point yet where we're quite comfortable with having confi-

medical information about individual patients on the Internet", said Dr. Baer, "I think there have been well-publicized issues about hacking and about privacy and about holes in browsers, back doors into databases and sale of information that was meant to be confidential". For these same reasons, many physicians believe that online billing has potential risks. If measures can be taken to assure security, the use of online billing should increase. Presently, many physicians who have adopted billing by modem pay service charges to Bell Canada. They do so in order to get the assurance of security (through reputation) when using Bell's Internet Service, called Datapaet, to connect to government servers.

The survey reported that the two applications Canadian physicians were least motivated to incorporate into their practices were sending electronic mail to patients and writing online prescriptions. Only 1% of Canadian physicians wrote prescriptions online, and of the 99% who did not write online prescriptions, 55% indicated, "no or very little interest in using this service" in the future.

In Canada, while 23% of physicians have used e-mail to communicate with patients, 49% reported "no interest in this online service". Dr. Michelle Moss, a family doctor from Calgary, summarized the views of many reluctant physicians, "I find it an invasion of my privacy because I have e-mail only at home, and that's my time. I find what people will tend to do if they know they can e-mail me instead of coming for an office visit, is that they'll just e-mail me, and I don't want that."

Other physicians expressed fear that physician-patient communication might suffer because of the impersonal nature of electronic mail. Dr. Gillian Fisher, medical director of long-term care at Montreal's Jewish General Hospital, said "e-mails are very easily misinterpreted. You can say something with a smile on your face, and it comes over quite differently as a blank statement over an e-mail." As with billing over the Internet, sending confidential patient information via e-mail also raises concerns over security.

From an international perspective, the Health on the Net Federation surveyed 1,863 health care workers in Europe and found that 32% of physicians and 22% of nurses regularly use the Internet.² The general trend from 1997 to 1999 showed a 40% increase in the proportion of female users. Females also comprised the majority of Internet users (63%). In this European study, the most common uses of the Internet by physicians included:

1. Accessing disease information	95%
2. Reading online medical journals	88%
3. Obtaining drug information	86%
4. Visiting medical association websites	80%
5. Consulting with colleagues in own country via e-mail	70%
6. Seeking information pertaining to health	50%
7. Consulting with colleagues in other countries via e-mail	45%
8. Insurance billing claims	25%

Interestingly, when asked whom health care workers were seeking online information for, 29% said it was for patients, 27% said it was for themselves and 25% said it was for a family member. This suggests that 1 in 4 physicians use the

Internet for their own health concerns or health concerns of their family. This demonstrates the significant degree of trust that physicians are placing on the information that can be found online.

Although it appears that trust in quality of medical information accessible over the Internet is growing, there remain many concerns over the accuracy of information that patients are accessing and the potential implications of this for the physician-patient relationship. The Medical Post survey highlighted such concerns, as voiced by Dr. Tom Baitz, an Ontario internist. He perceives that patients, in general, have a strange lack of trust of physicians, which he partly attributes to the popularity of alternative forms of health care. With the proliferation of "speculative medical information" now available online, he fears the divergence between physicians and patients will only widen. Regarding the proliferation of information online, Dr. Baitz says, "My worry is that when they [patients] get selected information, which may be contrary to accepted medical views, then what will they do? Will they come to us [physicians] to clarify it, or will they make the assumption that we physicians gave them the 'wrong' information? ...I'm afraid that the patient who comes to ask the question is the tip of the iceberg, the one-tenth who does take the trouble to ask me for clarification. But what about the other nine-tenths who remain submerged below the water level that I do not see, who do not ask the question?"

Today, more than one in five Canadians use the Internet to access health information, reflecting the growing trend of patients demanding more control over their own health and welfare.¹ Seven out of ten Canadian physicians reported having at least one patient in the past month mention or show medical counsel they found online.¹ When asked about the effect of patients reading online material the *Medical Post* survey showed that the majority of Canadian physicians said that this trend had a "neutral or negative impact on patient general well being". The major concern of many physicians was that misinformation could lead to poor compliance to medically proven therapies.

To circumvent patient misinformation, websites should be scrutinized to determine the use of proper research methods and to expose bias in presentation. *Health on the Net* is a widely known non-profit organization that uses certain criteria to decide whether a website receives its endorsement.² Among the requirements to be endorsed are that a website must be up-to-date, have obtained its information from health professionals, give references and source data, denote authorship, and identify sponsorship. They suggest those searching for information online to use university-based or a reputable medical association websites, where information is peer-reviewed. Commercial sites that stand to profit from a product, and personal websites providing anecdotal results, are not approved. Finally, Internet users should note the country of origin of the website; standard treatment protocols and drug approvals differ from one country to the next.

On the other hand, patients who are able to access reliable and accurate medical information can often save their doctor from having to do the research themselves. This information can also give patients a better appreciation of their condition

and improve treatment compliance, as well as their understanding and acceptance of their prognosis.^{1,3} Most importantly, such knowledge may stimulate open discussion with their physician.¹ It is critical that physicians do not dismiss what patients discover on the Internet, but instead use patients' research to explain why a particular course of treatment is recommended.³ This can build trust and confidence in the patient-physician relationship.

The reality of medical practice today is that many patients demand that they be included as active participants in medical decision-making. Physicians should be proactive and engage their patients in discussion when they bring information to the office. Physicians should make patients aware that medical information discovered online should always be reviewed in consultation with a doctor. Physicians need to explore the World-Wide Web themselves to see what their patients may encounter and to find reliable medical information that they can recommend to their patients.

The potential value of the World-Wide Web to physicians is enormous. Everything from administrative uses, continuing medical education, and patient care can be serviced over the Internet. While use by patients may present some difficulties, especially in treatment compliance and patient-physician trust, if physicians take the time to address patient concerns, put findings into context, and direct patients to useful sources, the Internet will enhance medical practice in the future.

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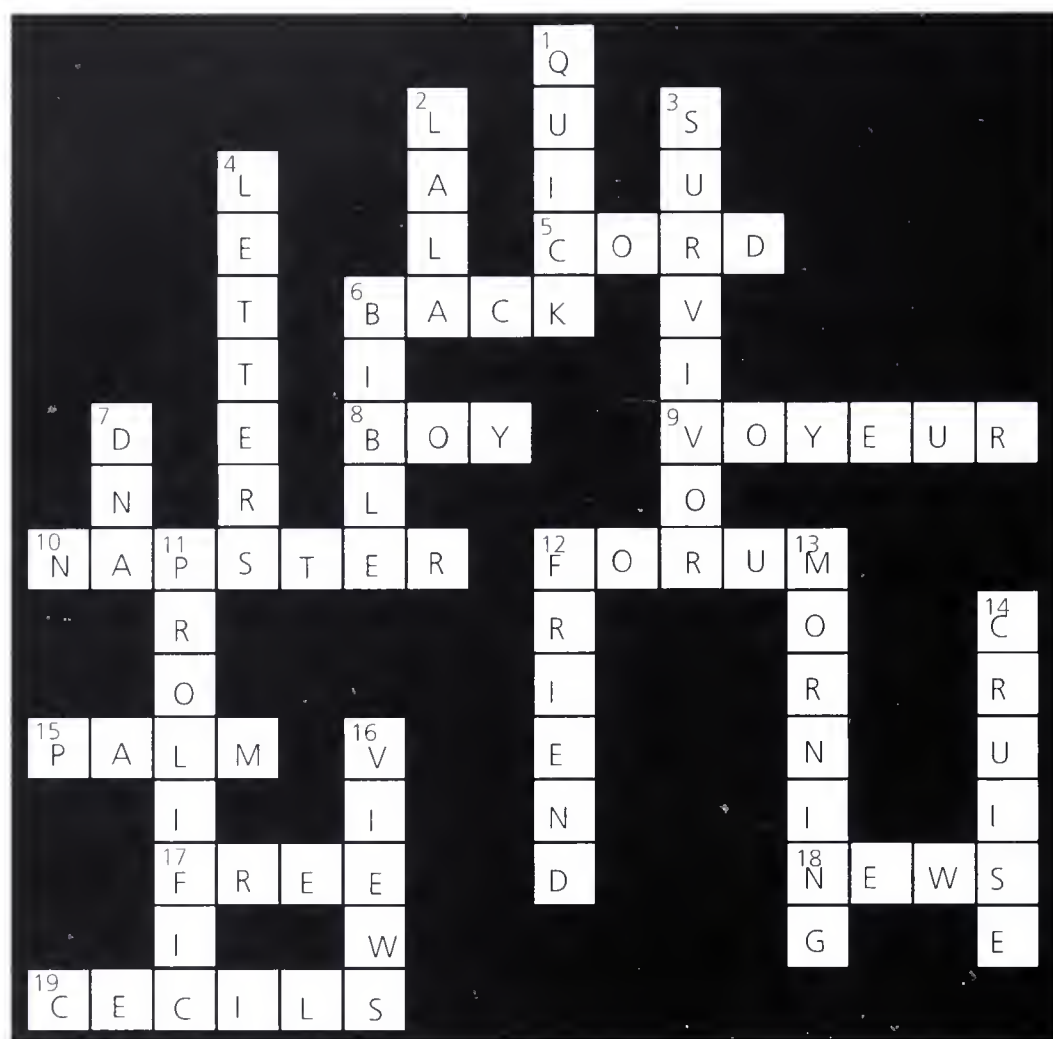
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A Rare But Deadly Disease

Yael Friedman, M.Sc. (OT3)
Andrea K. Boggild, M.Sc. (OT3)
Lesley Lee, M.D.*

Case Presentation

A 50-year-old man with a history of type II diabetes mellitus was admitted for management of his blood glucose levels and elective insertion of an AV fistula in his right arm for hemodialysis.

Past Medical Health

The past medical health is notable for a ten-year history of poorly controlled type II diabetes with associated complications, including diabetic retinopathy of the left eye and chronic renal insufficiency, as indicated by a creatinine level of 400 $\mu\text{mol/L}$ seven months prior to the current admission. There was also a history of sickle cell anemia, and a ten-year history of hypertension and hyperlipidemia. The patient had no known drug allergies and was an ex-smoker with no alcohol history. His family history was non-contributory.

Current Admission

Insertion of the AV fistula was complicated by intraoperative hyperglycemia (blood glucose 33 mmol/L). Consequently, he was admitted to the nephrology service to manage his blood glucose with an insulin drip. During this time, the patient reported left eye pain of six weeks duration with loss of vision in the left eye for four weeks. He reported that he had been examined by an ophthalmologist who had diagnosed elevated left intraocular pressure and treated him with eye drops (Betagan 0.25% and Alphagan 0.3%). The patient had not used the eye drops since admission and reported increasing pain in the left eye the following day.

When examined, the patient was uncomfortable, but had stable vital signs. The left pupil was dilated and non-responsive to light. Visual acuity was impaired with a left ptosis. The left forehead and temporal region were tender upon palpation. The right eye was normal, as were the rest of the general and neurological exams. A number of laboratory investigations had been carried out upon admission (see Table 1). The Betagan/Alphagan eye drops were restarted and the pain appeared to improve.

However, over the next 72 hours, the pain recurred and he was re-examined. He was mildly febrile (temperature 38°C), with a heart rate of 70 bpm and a blood pressure of 180/90 mmHg.

On this assessment, the patient had difficulty following commands. The left pupil remained dilated with chemosis and proptosis, and left ocular movements were absent. There was no audible periorbital bruit. The right eye remained normal.

Lesion Localization

When a patient presents with neurological abnormalities, one must localize the lesion at the beginning of the diagnostic process. This patient's symptoms could be related to an optic-globe pathology such as glaucoma, a slowly progressive, insidious optic neuropathy usually associated with chronic elevation of intraocular pressure. However, such pathology would not be associated with restricted extraocular movements (EOMs) or a fever, as were manifested in this patient. A lesion in the brainstem, causing dysfunction of cranial nerves III-XI, can result in restricted EOMs, but would not explain the pain, the unilaterality of the EOM restriction, and the chemosis. Similarly, a lesion in the cortex may result in a gaze preference but not a painful ophthalmoplegia.

What is the differential diagnosis for these clinical findings?

Presumptive Diagnosis

Cavernous Sinus Syndrome

Painful ophthalmoplegia can develop from pathology in the cavernous sinus. The cavernous sinus contains several important structures, including the intracavernous carotid artery, the sympathetic carotid plexus, cranial nerves III, IV and VI, and the ophthalmic division of the trigeminal nerve (V_1). The maxillary division of the trigeminal nerve (V_2) traverses the posteroinferior portion of the lateral cavernous sinus before exiting through the foramen rotundum.¹⁻³ The superior division of the oculomotor nerve (III) supplies the superior rectus and levator palpebrae superioris muscles, whereas the inferior division innervates the medial rectus, inferior rectus and inferior oblique muscles as well as the parasympathetic axons to the pupilloconstrictor muscle of the iris and the ciliary muscle.^{2,3}

Patients with cavernous sinus lesions typically present with the following symptomatology: periorbital or hemicranial pain, ipsilateral ocular motor nerve palsies, oculosympathetic paralysis and sensory loss in the distribution of V_1 . Thus, cavernous sinus syndrome is defined as involvement of two or more of CNs III, IV, VI, V_1 , V_2 or the oculosympathetic fibres, ipsilat-

*Division of Neurology, Sunnybrook and Women's College Health Sciences Centre

erally.^{3,4} There is a spectrum of conditions capable of causing a cavernous sinus syndrome; one must consider which of the possible diagnoses is/are consistent with the features of the clinical case at hand.

The causes of cavernous sinus pathology can be divided into five broad categories: vascular, traumatic, neoplastic, inflammatory and infectious. Vascular causes include intracavernous carotid aneurysm, posterior cerebral artery aneurysm, carotid-cavernous fistula (CCF) and carotid-cavernous thrombosis. Aneurysms of the intracavernous part of the internal carotid artery account for 3-5% of all intracranial aneurysms.⁵ These may be idiopathic, traumatic or associated with collagen disorders such as Marfan's and Ehlers-Danlos syndromes. The incidence of subarachnoid hemorrhage in untreated aneurysms has been reported as 1%.⁶ Traumatic aneurysms can result from blunt or penetrating trauma; there is usually an associated cranial fracture. Aneurysms resulting from trauma can be classified as "true" or "false." True aneurysms involve a partial disruption of the arterial wall with intact vessel layers. In contrast, false aneurysms, also known as pseudoaneurysms, are associated with a complete arterial wall disruption most likely resulting from stretching, sudden torsion or shearing forces.⁷ Presenting symptoms depend on the size and direction of extension of the aneurysm. Lateral extension is the most common, resulting in the classic symptomatology associated with cavernous sinus syndrome namely headache, ptosis and a slowly progressive unilateral ophthalmoplegia, as well as other symptoms.⁶ In this case, with no history of head injury prior to admission, aneurysm is an unlikely etiology.

Arteriovenous fistulas have been observed following trauma. CCFs are the most common and can be categorized into three subgroups: traumatic or spontaneous, high- or low-flow, and direct or indirect.⁸ The majority of traumatic CCFs are direct, resulting in a communication between the internal carotid artery and the cavernous sinus through a tear in the arterial wall. On the other hand, the majority of spontaneous CCFs are of the indirect (dural), low-flow type. CCFs have the potential to enlarge significantly, compressing adjacent structures and causing progressive neurological dysfunction. Death can ultimately result and is thought to occur due to arterial insufficiency and venous hypertension.⁸ Patients with direct, traumatic, high-flow CCFs present with proptosis, chemosis, ocular motor nerve palsies, retinopathy, periorbital bruits, increased intraocular pressure and tortuous, red conjunctival vessels.^{7,8} In this case, one of the diagnostic hallmarks of most CCFs,⁹ a periorbital bruit, was not audible.

On the other end of the spectrum, low-flow dural-cavernous fistulas most commonly occur spontaneously, and are due to communication between dural branches of the internal or external carotid arteries and the cavernous sinus or vessels in close proximity to the cavernous sinus. Patients with these types of fistulas present with more subtle clinical symptoms than those with direct CCFs, making diagnosis more difficult.

Intracranial cavernous hemangiomas represent an interesting benign lesion, in that they are classified as vascular malformations (accounting for 5-10% of intracranial vascular malformations), but also share features such as mass effects and specific radiological features with neoplasms. Most patients present

with ptosis, diplopia and facial numbness or neuralgia if V₂ and V₃ are involved. These tumors are distinguished by their hyperintense appearance in T2-weighted MRI scans.¹⁰

Cavernous sinus syndromes are often associated with an underlying neoplasm. In a study of 151 patients, Keane reported that tumors were the most frequent cause (30%) of cavernous sinus syndrome, followed by trauma (24%), self-limited inflammation (23%), and surgical trauma (11%); carotid aneurysms and fistulas, and infection were to blame in the remaining 12% of patients.⁴ In another study of 102 patients, neoplasms were the underlying cause of CSS in 70%.^{11,12} Neoplasms can be classified as primary, local metastases, or distant metastases. Primary benign intracranial tumors include pituitary adenomas, meningiomas, craniopharyngiomas, sarcomas, neurofibromas, neurolemas, chordomas, chondromas and giant-cell tumors. These tumors are usually associated with the involvement of a single cranial nerve for a prolonged period of time.⁴

Malignant neoplasms, including lymphomas,^{11,13,14} leukemias,¹⁵ myelomas,¹⁶ squamous cell carcinomas,¹⁷ renal cell carcinomas¹⁸ and melanomas,¹⁹ tend to cause more rapidly appearing neurological signs. Nasopharyngeal carcinoma, one of the most common tumors causing cavernous sinus syndrome, has certain characteristic associated features, such as a 2-3-fold male pre-

Table 1		
Variable	Value	Normal Range
Glucose (fasting)	33.2	4.0-6.0 mmol/L
Hematocrit	0.288	0.400-0.500 L/L
Hemoglobin	99	135-170 g/L
MCH	24.4	27-32 pg
MCHC	343	320-360 g/L
MCV	71.2	80-100 fL
Platelet count	290	150-400 x 10 ⁹ /L
RBC count	4.04	4.50-6.00 x 10 ¹² /L
RDW	21.9	10.0-14.5%
WBC count	16.5	4.0-11.0 x 10 ⁹ /L
Chloride	99	96-108 mmol/L
CO ₂ total	6	22-30 mmol/L
Potassium	5.2	3.5-5.0 mmol/L
Sodium	131	135-147 mmol/L
Urea	56.5	3.0-7.0 mmol/L
Creatinine	1320	44-106 µmol/L

proptosis and a varied clinical presentation of nasal obstruction, epistaxis, otitis media, proptosis, ipsilateral exophthalmia (dry eye), and the preferential involvement of CN VI.³

Inflammatory conditions can also cause cavernous sinus syndrome. Tolosa-Hunt syndrome (THS), caused by a non-caseating granulomatous inflammation, must be included in the differential diagnosis of painful ophthalmoplegia, but is a diagnosis of exclusion. Case reports have defined the following diagnostic criteria for THS: (a) gnawing periorbital pain occurring before, with or after the (b) appearance of an ophthalmoplegia resulting from lesions of CN III, IV and VI, (c) frequent dysfunction of the optic, oculosympathetic and first two divisions of CN V, (d) signs and symptoms that show spontaneous remission or recurring at intervals of months or years, and (e) no evidence of involvement of structures outside the cavernous sinus.³

Besides THS, and other granulomatous inflammatory conditions such as sarcoidosis and Wegener's granulomatosis,²⁰ inflammation can be attributed to a variety of infectious organisms, including bacteria, viruses and fungi. Reactivation of latent varicella zoster virus may result in shingles, which if present in the distribution of V_1 , causes a dermatomal pattern of painful ocular symptoms such as raised intraocular pressure, ocular motor nerve palsies and neuralgia. Bacterial infections, such as tuberculosis, have been associated with cavernous sinus syndrome.^{21,22} Although tuberculomas in the cavernous sinus are exceptionally rare, tuberculosis must be considered in the differential diagnosis in the presence of risk factors since, in developing countries, nearly 20% of intracranial masses have tuberculous origin.²¹ Fungal infections, which have been associated with cavernous sinus syndrome and other invasive diseases, are often difficult to distinguish from bacterial or other infections and thus remain elusive to diagnosis.

Clinical Diagnosis

Mucormycosis

Mucormycosis is a fungal infection caused by organisms belonging to the Order *Mucorales* and the Class *Zygomycetes*.^{23,26} It is most commonly caused by fungi from the genera *Rhizopus*, *Mucor* and *Absidia*. These fungi have a widespread geographic distribution and are ubiquitous in air, soil, vegetable matter and bread mold.^{23,25} *Mucorales* spores have been cultured from the oral and nasal mucosae of people without the disease.²³ Mucormycosis has diverse clinical manifestations that are classified as rhinocerebral, disseminated, pulmonary, gastrointestinal and cutaneous. The rhinocerebral (RCM) form is the most common and the most likely to be fatal. Typically, the infection begins in the paranasal sinuses and rapidly spreads to the orbit, cavernous sinus and brain parenchyma.^{23,25,27}

RCM usually occurs in patients with debilitating disease, most commonly diabetes mellitus (60-80% of cases).²³ The majority of diabetic patients with mucormycosis are poorly controlled, although cases in well-controlled diabetics have been reported. Diabetics are predisposed to mucormycosis because their plasma contains weakened neutrophils and monocytes (thereby resulting in reduced phagocytosis), decreased fungal inhibitory factors and increased levels of unbound iron, all of which have been reported to enhance fungal growth.²² Additionally, the

presence of an active ketone-reductase system allows *Mucorales* to thrive in a glucose-rich and acidotic environment.^{23,25} In contrast, normal hosts are able to destroy the fungal spores via phagocytosis. Other predisposing conditions include certain hematologic diseases (leukemia, lymphoma, neutropenia), renal disease, immunosuppression, organ transplantation with chronic, high-dose corticosteroid treatment, malnutrition, and desferoxamine therapy.^{23,29} Interestingly, HIV has not been found to be an independent risk factor for developing mucormycosis.²³

RCM develops in three stages. The first stage occurs following the inhalation of aerosolized fungal spores. The paranasal sinuses are infected and necrotic lesions of the nasal mucosa and turbinates appear. Within the first 72 hours, the most common signs and symptoms include fever, decreased vision and facial swelling.²³ The second stage, orbital infection, occurs either by direct extension through the maxillary sinus or through the blood vessels. There is a distinct proclivity for vessel wall invasion, producing thrombosis, ischemia and infarction, or dissecting aneurysms. Vascular occlusion produces an acidotic tissue ideal for fungal growth.^{23,24} During this stage, patients will typically present with proptosis, chemosis and ophthalmoplegia. Visual loss can occur as a result of central retinal artery occlusion.^{23,25} In the third stage, the infection spreads intracranially via the cribriform plate or orbital apex.

Laboratory evaluation will often be consistent with diabetic ketoacidosis or hyperglycemia and a neutrophilic leukocytosis. Examination of the CSF reveals elevations in glucose and protein. Blood cultures are rarely positive.²³ Radiographic imaging may be helpful in establishing the extent of sinus, orbital or intracranial infection.³⁰

Intravenous amphotericin B has significantly improved the survival rates of patients with mucormycosis. Adjuncts to systemic antifungal chemotherapy include management of acidosis, minimizing immunosuppression in compromised patients and radical surgical resection.²³⁻²⁸ Even with early diagnosis and aggressive surgical and medical management, long-term survival after RCM is uncertain, and the mortality rate is 20%.²⁴

Patient Outcome

By the seventh day post-admission, the patient's condition continued to deteriorate and his fever had elevated. Upon examination, his left pupil remained fixed and dilated. There was a left-sided ptosis, significant proptosis and no EOMs of the left eye. A left CN VII palsy, reduced deep tendon reflexes, decreased sensation on the right side in the distribution of V_1 - V_3 , hoarseness and reduced gag reflex were also noted. Lumbar puncture revealed pus cells but not bacteria, an elevated CSF glucose, protein and WBC count, mainly due to neutrophilia. Empiric therapy with broad spectrum antibiotics and antifungals was initiated and an MRI was ordered. The following morning, the patient had a cardiac arrest and could not be resuscitated. Subsequently, an autopsy was performed.

Pathological Discussion

The brain weight at autopsy was 1340 grams. In addition to the brain, samples of the optic nerves, retinae and cavernous sinuses were taken. Gross examination of the brain showed necrosis of the orbitofrontal and temporal areas, especially on the left. Microscopic examination revealed numerous foci of

neutrophilic infiltrate surrounding fungal hyphae in numerous sections of the cerebrum, particularly the orbitofrontal and temporal lobes. Areas of infarction with numerous ischemic neurons and fungal elements were identified in the left inferior temporal and orbitofrontal lobes. Multiple micro-abscesses involving the internal capsule, cerebral peduncle and midbrain were seen. There was fungal involvement of the left CN III, infarction of the left extraocular muscles and fungal invasion of the optic nerve. Fungi were also observed in the nasal sinuses, the left paranasal sinus and the left sphenoid sinus. The left cavernous sinus appeared to be completely filled with pus and fungal elements. All of the nerves traversing this structure, including the trigeminal ganglion, were invaded by fungal elements. In addition, heavy fungal infiltration had destroyed the intima and media of the cavernous segment of the internal carotid artery. The fungal hyphae were varying in caliber and non-septate, with mostly right-angle branching. These fungal hyphae were better highlighted with PAS staining (Figure 1).

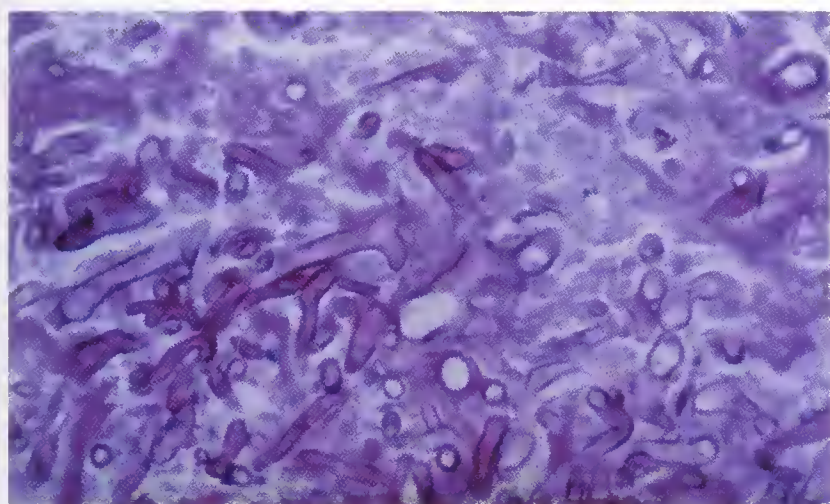


Figure 1. PAS stain of non-septate fungal hyphae in the cavernous sinus.

Pathological Diagnosis

Rhino-orbito-cerebral Mucormycosis

In summary, a diagnosis of rhino-orbito-cerebral mucormycosis was made based on the following findings:

- Involvement of the nasal, paranasal, sphenoid and cavernous sinuses on the left, including the carotid artery, adjacent cranial nerves and the trigeminal ganglion,
- Infarcts of the left optic nerve, oculomotor nerves, oculomotor muscles and retina, and
- Micro-abscesses with infarction of the inferior fronto-temporal lobes and midbrain.

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Case Reports from the University of Toronto Faculty of Medicine

Piero Tartaro, B.Sc. (OT3)
Steven W H Hwang, B.Sc. (OT3)
Shoba Subramanian, B.Sc. (OT3)

Case 1

Robert A. Mustard, Jr. B.Sc., M.D., F.R.C.S.(C), F.A.C.S
Department of Surgery, St. Michael's Hospital

Ralph E. Warren, M.D., F.R.C.P.C., D.T.M.&H.
Division of Gastroenterology, St. Michael's Hospital

A 65-year-old woman complained of abdominal cramps and bright red blood in her stool that started 2 months prior to presentation. Her hemoglobin was normal at 137g/L, and her remaining CBC results, TSH, creatinine and liver function tests were also normal. Stool samples were negative for bacterial pathogens, however numerous RBC and a few WBC were detected. On examination, no palpable mass or tenderness was elicited and the digital rectal exam did not reveal any abnormalities. Sigmoidoscopy was performed and a mass was localized 20cm into the sigmoid colon (Figure 1.1).

What is the diagnosis?

What is the next step in managing the patient?

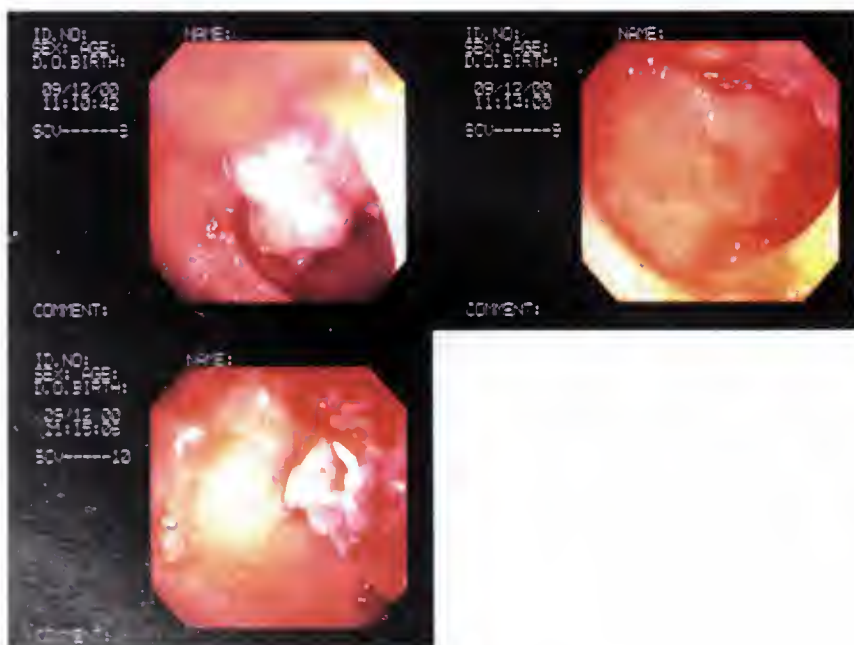


Figure 1.1.

Case 2

Charles H. Tator, C.M., M.D., Ph.D., F.R.C.S.(C), F.A.C.S.
Department of Surgery, Division of Neurosurgery, Toronto Western Hospital

A 51-year-old man is referred to you because of progressive lower back pain. He is a bus driver, who upon trying to lift a passenger aboard, experienced severe lower back pain. Over the past 7 months, the pain has worsened and has spread to both his legs. He finds the pain is greater with exercise and had difficulty voiding his urine once. On examination you note that he has paravertebral muscle spasms of the lumbar spine and mild right quadriceps weakness. His knee reflexes are 2+ bilaterally, he has downgoing plantar reflexes, he has no sensory loss and no clonus. He has had some alleviation of the pain from seeing a chiropractor for "disc problems", but the pain still persists. An MRI is performed to investigate the spinal cord and is shown below (Figures 2.1 and 2.2 - T2 weighted MRI, sagittal and axial views).

What is the most likely diagnosis?

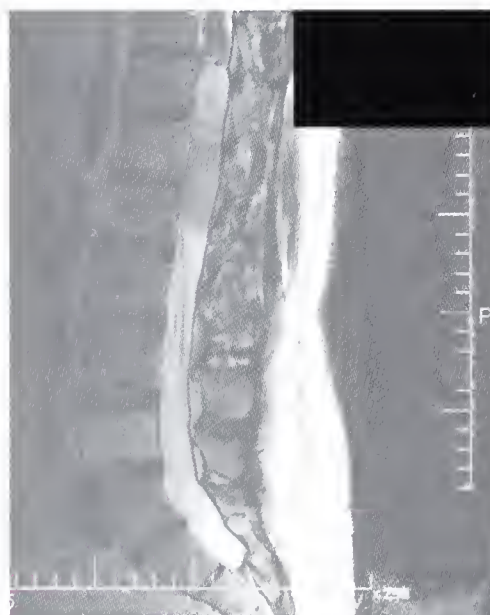


Figure 2.1. T2-weighted parasagittal MRI image of the tumour and spinal cord. The tumour extends from T11 to L1.

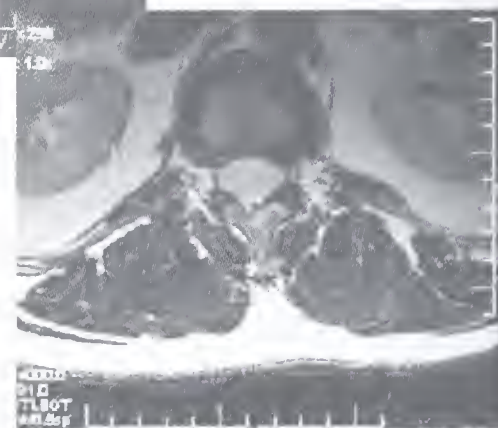


Figure 2.2. T2-weighted axial MRI image of the tumour cross-section. The tumour occupies almost the entire spinal canal.

Case 3

Filomena Meffe, M.D., F.R.C.S. (C), M.Sc.
Department of Obstetrics and Gynaecology,
St. Michael's Hospital

A 23-year-old woman, G5P1A3, at 20 weeks gestational age, came for her routine 20 week fetal anatomy ultrasound scan. A series of ultrasound images are demonstrated below. Her pregnancy had been uneventful and her maternal serum screen, done at 16 weeks, was reported as negative. Her past obstetrical history included 3 previous spontaneous abortions and one emergency Cesarean delivery at term for a placental abruption and non-reassuring fetal tracing. On receiving the report of her ultrasound scan, her obstetrician referred her to a high risk obstetrical centre and advanced neonatal centre for further evaluation and care.

What is the diagnosis?

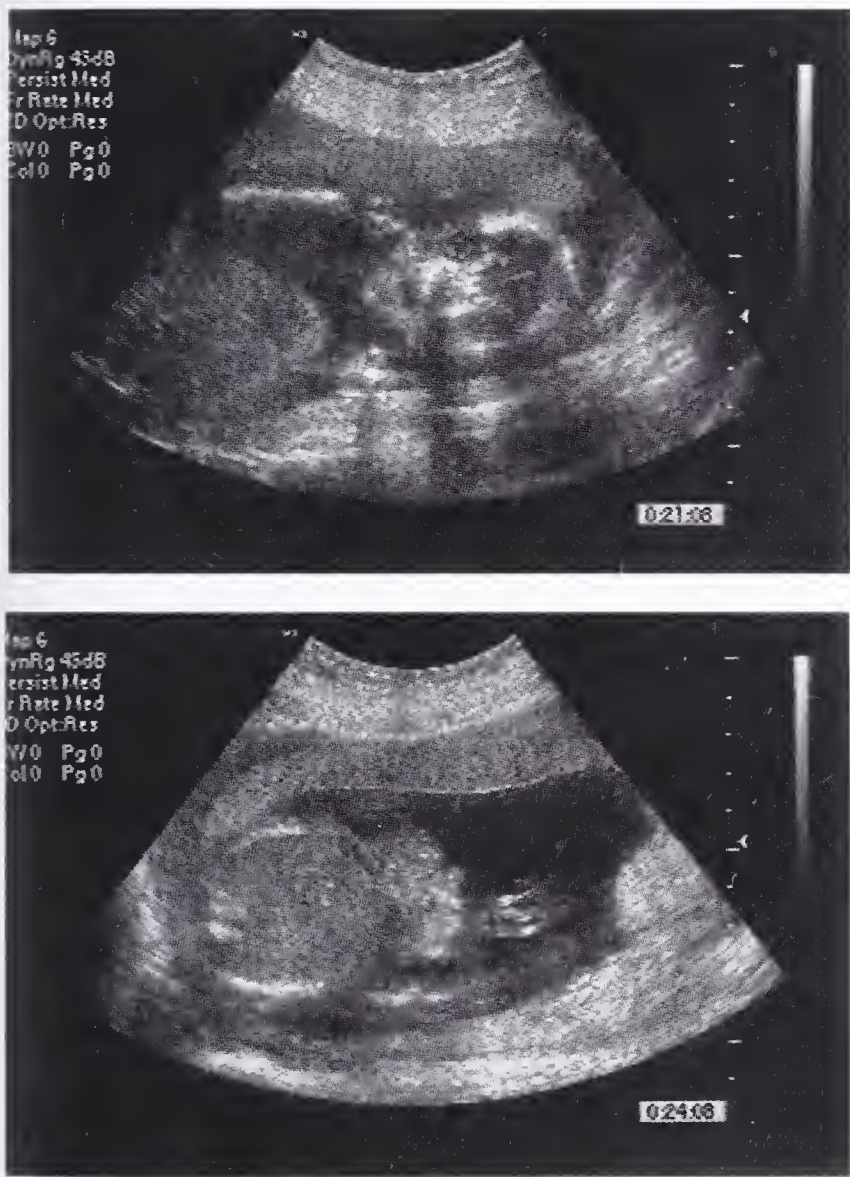


Figure 3.1. Ultrasound scan at 20 weeks

Case 4

Nigel Beasley M.B.B.S., F.R.C.S.(Eng) and Jeremy Freeman M.D.,
F.R.C.S.(C)
Department of Otolaryngology, Mount Sinai Hospital

A 45-year-old woman of Southern Chinese origin presented with a three month history of recurrent epistaxis, left sided hearing loss, nasal obstruction and a mass in the left neck. On examination a firm 3 cm mass was palpable in the posterior triangle of the left neck and on rigid nasal endoscopy a fleshy lesion was visible filling the nasopharynx. Examination of the left ear revealed a dull, retracted tympanic membrane with fluid behind.

What is the diagnosis?



Figure 4.1. Axial MRI scans



Figure 4.2. Axial MRI scans

Case 5

Shah Gupta MD, PhD, FRCSC, Filiberto Altomare MD, FRCSC
Department of Ophthalmology, St. Michael's Hospital,
University of Toronto.

Four weeks after glaucoma filtration surgery in the left eye, a 66-year-old black gentleman presented with markedly reduced vision in the same eye. His past medical history included long-standing insulin-dependent diabetes mellitus and hypertension. On examination, best corrected visual acuity was 20/25 in the right eye and 20/300 in the left eye. Fundus examination of the right eye demonstrated glaucomatous disc changes.

What is the diagnosis?



Figure 5.1. Left eye fundus examination

Figure 1.2.

Case 6

Dr. John Wedge, M.D., Department of Surgery, The Hospital for Sick Children

A 14-month-old girl was referred to the Hospital for Sick Children after a family member had noticed that the infant walked with a limp and seemed to have a short left leg. The baby had a normal delivery without any complications and began walking at 13 months. There was no family history of any musculoskeletal deformities. Physical examination revealed a short-leg gait with a lurch to the left, asymmetrical thigh creases, limited abduction with prominence of the adductor longus tendon, a positive Galeazzi sign with shortening of the left thigh, a leg length discrepancy, and wasting of the muscles of the left buttock and proximal thigh. Figures 6.1 and 6.2 show X-rays taken at the hospital.

What is the diagnosis?



Figure 6.1. X-ray of hip



Figure 6.2. X-ray of hip

Case 7

Dr. Ted Gerstle, M.D., Department of Surgery, The Hospital for Sick Children

A 5-month-old boy was brought to a community hospital with respiratory difficulty and a sporadic dry cough. He had recently been discharged from the hospital on salbutamol (Ventolin) and budesonide (Pulmicort) puffers after having been treated for 5 days for bronchiolitis. A chest X-ray revealed a mass in the right upper mediastinum and he was referred to the Hospital for Sick Children for further evaluation. Examination revealed a healthy child with stridor since birth that increases in the evening and disappears when asleep. There was no fever, no cyanosis, no feeding difficulties, and good air entry bilaterally. A CT scan showed a round, non-enhancing, complex, cystic mass with multiple septations in the right middle mediastinum compressing the distal aspect of the trachea (Figure 7.1).

What is the differential diagnosis?

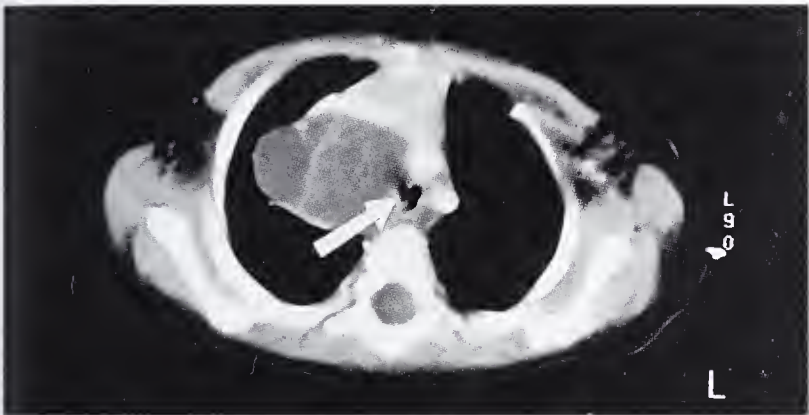


Figure 7.1. CT scan before any treatment

Case 8

Dr. Sender Herschom, M.D., F.R.C.S.C., Department of Urology, Sunnybrook and Women's College Health Sciences Centre

A 48-year-old male has been experiencing recurrent bouts of urinary frequency, urgency, dysuria, variable low-grade fever, and occasional low-back pain since puberty. These episodes occur approximately three times a year and have recently become more frequent. Although each episode has been treated successfully with TMP/SMX, they continue to recur. Physical examination revealed a palpable, tender prostate. Otherwise, he is a healthy individual.

What is the diagnosis?

**Get the
Knowledge**

**Use
the power**

**Drive the
wheels!**

expect**more**

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And the diagnosis is...

Case 1

Diagnosis: Adenocarcinoma of the sigmoid colon (polypoid mass)

Prior to resecting the mass, the patient underwent a CT scan (Figure 1.2) and chest X ray to stage the tumor. As a result of these further examinations, a much larger mass (8 cm x 8 cm x 1.7 cm) was found in the cecum which was likely the primary cause of her symptoms. These results underline the importance of performing colonoscopy to look for additional polyps or a second primary in patients like this one. Approximately 8% of colorectal cancers occur in the descending colon and approximately 35% are found in the sigmoid colon which can be visualized and biopsied by flexible sigmoidoscopy. The remaining 38% of neoplasms arise in the cecum or ascending colon which may be visualized by colonoscopy. One percent of colorectal cancers discovered have more than 1 primary lesion and thus warrant a complete investigation prior to initiating surgical treatment.

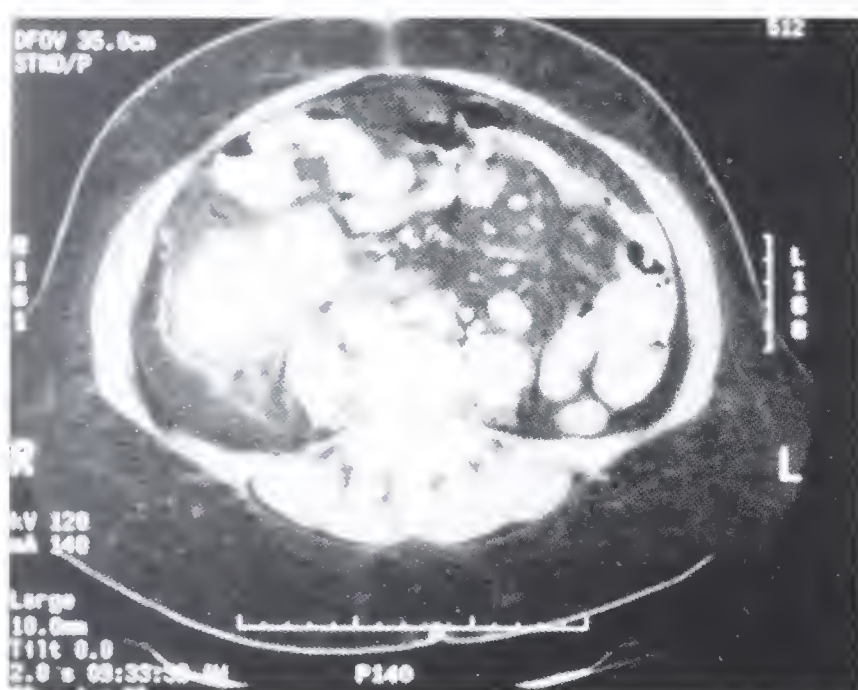


Figure 1.2.

Case 2

Diagnosis: Myxopapillary ependymoma

In the adult, ependymomas mostly occur in the spinal cord whereas in pediatric patients, they tend to develop in the 4th ventricle. Ependymomas tend to look uniform and well-demarcated on radiological investigation and often have pseudorosettes, rosettes, or blepharoplasts (basal bodies of cilia) present on histological examination. Furthermore, ependymomas arising in the filum terminale are myxopapillary because they secrete mucin and tend to be benign (only 2.4% are high-grade and progressive). In addition to their papillary component, they also contain epithelial-like elements that are lined by cuboidal or low columnar cells. Surgical intervention is often sufficient for myxopapillary ependymomas, but occasionally the ependymoma will spread beyond its capsule and seed in the subarachnoid space and encircle the nerve roots or spinal cord. In such cases, some of it cannot be resected and radiation therapy may be required to decrease the likelihood of metastatic progression. This patient underwent a T10-L2 laminectomy to remove the tumor, but some of it encircled the roots of the cauda equina, and thus was unresectable. He was subsequently referred for an oncological consult for administration of radiation therapy.

Case 3

Diagnosis: Gastroschisis

This fetus was diagnosed with gastroschisis, a relatively small (2-4 cm) paraumbilical defect involving all layers of the anterior abdominal wall associated with evisceration of abdominal organs. This defect may result from abnormal involution of the right umbilical vein or from disruption of the omphalomesenteric artery. Complications include bowel obstruction and/or ischaemia.

Sonographic findings include: (1) a full thickness abdominal wall defect located just to the right of a normal umbilical cord insertion site; (2) a variable amount of bowel protruding through the defect and floating in the surrounding amniotic fluid; and (3) a disproportionately large appearance to the eviscerated bowel relative to the abdominal cavity even though the defect itself is small and measuring less than 2 cm.

Prognosis for fetuses identified with gastroschisis is excellent with a mortality rate of less than 10%. Management usually involves maternal obstetrical care and fetal delivery at a high risk obstetrical centre or near a neonatal referral centre with experienced pediatric surgeons to facilitate prompt surgical correction of the abdominal defect. Some authors recommend elective Caesarean delivery to reduce risk of bowel trauma and contamination but others believe that vaginal birth is quite safe. Primary closure of the abdominal wall defect is usually performed within 2-3 hours of delivery, since prompt repair minimizes problems with bacterial contamination, sepsis, hypothermia, and metabolic acidosis. Recently, silastic spring-loaded devices called sylos have been used to cover the defect immediately after birth. They allow the skin to stretch and bowel edema to settle. Repair of the defect occurs a few weeks later.

Case 4

Diagnosis: Nasopharyngeal carcinoma with neck node metastases

A large mass can be seen in the nasopharynx extending into the left parapharyngeal space in Fig. 4.1, and the neck node metastasis are evident in Figure 4.2. The diagnosis was confirmed by biopsy of the nasopharyngeal mass in the clinic under local anaesthetic. The patient underwent concurrent chemotherapy and radiation with good early results. Nasopharyngeal carcinoma is particularly common in the Southern Chinese population and is associated with Epstein Barr Virus infection. One of the first symptoms may be recurrent epistaxis and all patients of Southern Chinese origin with this symptom should undergo nasal endoscopy to rule out nasopharyngeal carcinoma.

Case 5

Diagnosis: Malignant hypertensive retinopathy

The left fundus examination showed numerous retinal hemorrhages. Blood pressure was markedly elevated at 220/110. The patient was sent to the Emergency department where urgent blood pressure lowering treatment was initiated. Systemic investigations in the medical intensive care unit were negative for non-ocular end-organ effects of malignant hypertension. Two weeks later, after stabilization of his blood pressure, retinal hemorrhages were resolving, and visual acuity in the left eye had improved to its previous level of 20/70.

Vision threatening eye conditions with similar retinal vascular changes include diabetic retinopathy and retinal vein occlusion. Although it is less common, malignant hypertension can be a systemic cause of acute vision loss and often presents bilaterally. The detection of malignant hypertensive retinopathy requires

a high index of suspicion, a blood pressure measurement, and may be life saving.

Case 6

Diagnosis: Developmental displacement of the left hip

Physical examination paints a clinical picture very suggestive of developmental displacement of the hip (DDH). The radiographs confirm a dislocation of the left hip and reveal the acetabular dysplasia accompanying the dislocation. DDH is the accepted term for what was previously known as congenital dislocation of the hip. The new term more accurately reflects the dynamic nature of this disorder and the fact that a percentage of hips that are classified as normal at birth may actually become dislocated or subluxated as late as 6 to 10 months of age. Furthermore, DDH includes not only the dislocation and subluxation of the femoral head, but also the related secondary dysplasia of the acetabulum and proximal femur. It occurs in approximately 1 in 1000 live births and is more common in females, those with a positive family history, and babies born with a breech presentation. In addition, certain cultural customs that involve maintaining the hips of newborn infants in extension and adduction increase the risk of DDH. The etiology is complex and not completely understood, but both environmental and genetic factors are important in its pathogenesis. Early diagnosis and appropriate treatment are crucial since as time goes on, the secondary changes as a result of the dislocation or subluxation become not only progressively more marked, but also progressively less reversible. Treatment varies according to age and the specific pathology. This baby underwent an open reduction followed by a Salter innominate osteotomy to correct the acetabular dysplasia. Salter's osteotomy of the innominate bone redirects the entire acetabulum so that its roof "covers" the femoral head anteriorly, laterally and superiorly where it is typically deficient.

Lack of awareness plus inadequate surveillance of the newborn for this very common developmental abnormality, makes DDH a significant public health problem.

Case 7

Diagnosis: Immature teratoma

Mediastinal cysts and tumors are relatively common in infants and children. The location of the mediastinal mass and the age of the patient are often useful factors to consider in arriving at a correct preoperative diagnosis; however, a definitive diagnosis requires biopsy or complete surgical excision of the mass. Based on the complex cystic nature of the mass, the differential diagnosis includes both mediastinal cysts and tumors, including the following:

Mediastinal cysts

- bronchogenic cysts
- thymic cysts
- enterogenous cysts
- desmoid cysts
- cystic hygroma
- pericardial cysts

Mediastinal tumors

- Hodgkin's disease
- non-Hodgkin's lymphoma
- neurogenic tumors
- thymoma
- teratomas
- other rare lesions

The boy underwent a right sided thoracotomy with complete excision of the mass (Figure 7.2). Note that the remaining anterior mediastinal mass in Figure 7.2 is not tumor, but normal thymus. Pathologic examination of the resected material revealed an encapsulated multicystic lesion comprised of tissue from all three germ layers. Although the tissue was mostly mature in nature, a small area of immature-appearing neuroepithelium was noted. Based on these pathologic features, a diag-

nosis of immature teratoma was made. The baby had an uncomplicated post-operative course and is being followed every few months with a CT scan and alpha-fetoprotein (AFP) level.

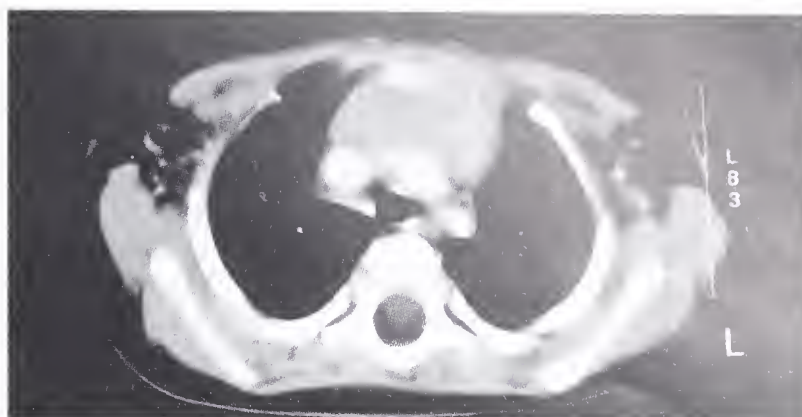


Figure 7.2. CT scan after excision of the tumour

Case 8

Diagnosis: Chronic bacterial prostatitis

This patient is experiencing recurrent urinary tract infections (UTI). Recurrent UTIs can be caused by either reinfection from outside the urinary tract or by bacterial persistence in a focus within the urinary tract. Although approximately 95% of recurrent UTIs in females are reinfections of the urinary tract, this is uncommon in males where bacterial persistence represents the majority of cases.

Recurrent UTIs with a low-grade fever, low back pain, and a palpable, tender prostate gland are consistent with chronic bacterial prostatitis. This is the most common cause of recurrent UTIs in men and is typified by relapsing recurrent UTI caused by persistence of the pathogen in the prostatic secretory system despite courses of antibacterial therapy. The diagnosis was established after culturing viridans streptococci from prostatic expressate. Since the prostate is an area which antimicrobial penetration is generally poor, the efficacy of antimicrobial agents is limited. Failure of complete elimination of the recurrent infections is common in patients with chronic prostatitis as in this patient who requires repeated antibiotic therapy for each recurrence.



LIPID TARGETS ACQUIRED^{1,*}

*A prospective, multicentre, randomised, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of cerivastatin 0.8 mg (n=776) or cerivastatin 0.4 mg (n=195) (of efficacy-valid patients: 63% males, 37% females; mean age=57.2 years) or placebo (n=199) once daily for 8 weeks in patients with primary hypercholesterolemia. Percent achieving NCEP recommended LDL-C levels for those patients treated with cerivastatin 0.8 mg ranged from 59%-84% depending on number of risk levels.

BAYCOL® (cerivastatin sodium tablets) is a HMG-CoA reductase inhibitor. BAYCOL® is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated Total-C and LDL-C levels in patients with primary hypercholesterolemia (type IIa) when the response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures alone has been inadequate. BAYCOL® is also indicated for the reduction of elevated cholesterol levels in patients with mixed (combined) hypercholesterolemia and hypertriglyceridemia (Type IIb), when the hypercholesterolemia is the abnormality of most concern.

It is recommended that liver function tests be performed before the initiation of treatment, and within 12 weeks after the initiation of therapy or elevation in dose, and periodically thereafter, e.g., semi-annually. If increases in ALT or AST show evidence of progression, particularly if they rise to > 3 x the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued. BAYCOL® is contraindicated during pregnancy and in nursing mothers. BAYCOL® is also contraindicated in concurrent treatment with gemfibrozil because of risk of rhabdomyolysis in patients with or without renal failure. Caution should be exercised in severe hypercholesterolemia patients who are also significantly renally impaired, elderly, or are concomitantly being administered digoxin, erythromycin or other products causing cytochrome P-450 mediated interactions.

Please see prescribing information for detailed safety profile and important information on potential drug interactions.

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ACTION AND CLINICAL PHARMACOLOGY

BAYCOL® (cervastatin sodium) is an entirely synthetic, enantiomerically pure cholesterol-lowering agent and is structurally similar to the fungal derivatives of this therapeutic class.

Cervastatin is a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. The inhibition of cholesterol biosynthesis by cervastatin reduces the level of cholesterol in hepatic cells, which stimulates the synthesis of low density lipoprotein (LDL) receptors, thereby increasing the uptake of cellular LDL particles. The end result of these biochemical processes is a reduction of plasma total cholesterol (Total-C) and low density lipoprotein cholesterol (LDL-C).

Cervastatin is rapidly absorbed following oral dosing. The absolute bioavailability of cervastatin sodium tablets is 60% compared to oral solution. The pharmacokinetics of cervastatin are linear over the dose range of 0.05 to 0.4 mg. Cervastatin is >99% bound to plasma proteins. The elimination half-life is in the range of 2 to 4 hours; consequently no drug accumulation with once daily dosing is observed. The pharmacokinetics of cervastatin are similar under fed and fasted conditions.

When ¹⁴C-cervastatin was given as an oral solution, the mean urinary excretion of total radioactivity was 24% of dose, while a mean of 70% was excreted in the feces. Thus, biliary secretion is a major pathway of drug (or metabolite) elimination. Only negligible quantities of ¹⁴C were associated with unchanged drug, indicating extensive metabolism. Cervastatin is metabolized via a dual metabolic pathway utilizing at least two cytochrome P-450 isoenzymes, CYP2C8 and CYP3A4. If one of the metabolic pathways (e.g., CYP3A4) is blocked, cervastatin is metabolized, although not completely in some cases, by the alternate metabolic route. Three metabolites have been identified, and M1 and M23 are present in plasma, urine and feces, whereas M24 is present in urine and feces only. Plasma concentrations of all identified metabolites are substantially lower than those of parent drug, and the elimination half-lives are similar. Therefore, while some metabolites have pharmacologic (i.e., HMG-CoA reductase inhibitory) activity, they do not contribute significantly to the overall efficacy of cervastatin.

INDICATIONS AND CLINICAL USE

BAYCOL® (cervastatin sodium) is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated Total-C and LDL-C levels in patients with primary hypercholesterolemia (types IIa and IIb) when the response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures alone has been inadequate. BAYCOL® is indicated for the reduction of elevated cholesterol levels in patients with combined hypercholesterolemia and hypertriglyceridemia, when the hypercholesterolemia is the abnormality of most concern.

Prior to initiating therapy with BAYCOL®, secondary causes for hyperlipoproteinemia, such as obesity, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy (e.g., some anti-hypertensive agents) or alcoholism, should be excluded. A lipid profile should be performed to measure Total-C, high density lipoprotein cholesterol (HDL-C) and triglycerides. For patients with total triglycerides less than 4.52 mmol/L (400 mg/dL), LDL-C can be estimated using the following equations:

$$LDL-C \text{ (mmol/L)} = \text{Total-C} - [(0.37 \times \text{Trig}) + HDL-C]$$

$$LDL-C \text{ (mg/dL)} = \text{Total-C} - [(0.16 \times \text{Trig}) + HDL-C]$$

When total triglyceride levels exceed 4.52 mmol/L (400 mg/dL), this equation is less accurate and LDL-C concentrations should be directly measured by preparative ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases, BAYCOL® is not indicated.

Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patient's response to therapy.

BAYCOL® has not been studied in conditions where the major abnormality is elevation of chylomicrons, very low density lipoprotein (VLDL), or intermediate-density lipoprotein (IDL), i.e., hyperlipoproteinemia types I, III, IV or V.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions: The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Cervastatin is metabolized via a dual metabolic pathway utilizing at least two cytochrome P-450 isoenzymes, CYP2C8 and CYP3A4. If one of the metabolic pathways (e.g., CYP3A4) is blocked, cervastatin is metabolized, although not completely in some cases, by the alternate metabolic route (see WARNINGS, Muscle Effects; PRECAUTIONS; DRUG INTERACTIONS, Cytochrome P-450 Inhibitors).

(For more information on the metabolism of cervastatin in humans, see ACTION AND CLINICAL PHARMACOLOGY.)

Hepatic Effects: In clinical trials, persistent increases of serum transaminase values to more than 3 times the upper limit of normal (ULN) (occurring on two or more, not necessarily sequential, occasions) have been reported in <1.0% of patients treated with cervastatin sodium. Most of these abnormalities occurred within the first 6 weeks of treatment, resolved after discontinuation of the drug, and were not associated with cholestasis. In most cases, these biochemical abnormalities were asymptomatic.

It is recommended that liver function tests be performed before the initiation of treatment, and within 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter, e.g., semiannually. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. It increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to >3 times the ULN and are persistent, the dosage should be reduced or the drug discontinued.

The drug should be used with caution in patients with a history of liver disease or heavy alcohol ingestion (>14 drinks/week).

Active liver disease or unexplained transaminase elevations are contraindications to the use of BAYCOL® (cervastatin sodium); if such conditions develop during therapy, the drug should be discontinued (see CONTRAINDICATIONS).

Muscle Effects: Myopathy, defined as muscle aching or muscle weakness, associated with increases in plasma creatine phosphokinase (CPK) values to greater than 10 times the ULN was rare (<0.2%) in cervastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased if therapy with cyclosporine, fibric acid derivatives, erythromycin, niacin (nicotinic acid) in lipid-lowering doses, nefazodone or azole antifungals is administered concurrently. The benefits and risks of combined therapy should be carefully considered (see PRECAUTIONS; DRUG INTERACTIONS).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria have been reported with other HMG-CoA reductase inhibitors. BAYCOL® therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. BAYCOL® should be temporarily withheld in any patient experiencing an acute or serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine or electrolyte disorders; or uncontrolled epilepsy.

PRECAUTIONS

General: The effects of cervastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality or total mortality have not been established.

Before instituting therapy with BAYCOL® (cervastatin sodium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND CLINICAL USE). The patient should be advised to inform subsequent physicians of the prior use of BAYCOL® or any other lipid-lowering agent.

Effect on Lens: Current data from clinical trials do not indicate an adverse effect of BAYCOL® on the human lens.

Use in Homozygous Familial Hypercholesterolemia: Cervastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. Most HMG-CoA reductase inhibitors are less or not effective in this subgroup of hypercholesterolemic patients.

Effect on Lipoprotein (a): In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in the Lipoprotein (a) [Lp(a)] levels. Therefore, until further experience is obtained from controlled clinical trials, it is suggested that measurements of serum Lp(a) be followed up in patients placed on BAYCOL® therapy.

Effect on CoQ₁₀ Levels (Ubiquinone): Significant decreases in circulating ubiquinone levels in patients treated with other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not yet been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure.

Hypersensitivity: An apparent hypersensitivity syndrome has been reported rarely with other HMG-CoA reductase inhibitors. This has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leucopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocyte sedimentation rate (ESR) increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, BAYCOL® should be discontinued if hypersensitivity is suspected.

Use in Pregnancy: BAYCOL® is contraindicated during pregnancy (see CONTRAINDICATIONS).

Safety in pregnant women has not been established. Atherosclerosis is a chronic process and discontinuation of lipid metabolism regulators during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Cervastatin sodium should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this drug, cervastatin sodium should be discontinued and the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers: Based on preclinical data, cervastatin sodium is present in breast milk in a 1.3:1 ratio (milk: plasma). It is not known whether cervastatin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, women taking BAYCOL® should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Limited experience with the use of other HMG-CoA reductase inhibitors is available in children. Safety and effectiveness of BAYCOL® in children have not been established.

Geriatric Use and Gender: The effect of age on the pharmacokinetics of BAYCOL® was evaluated. Results indicate that for the general patient population, plasma concentrations of BAYCOL® do not vary as a function of age. A slight increase in plasma cervastatin levels was observed in females (approximately 12% higher for C_{max} and 16% higher for AUC).

Use in Patients with Impaired Renal Function: No dose adjustment is necessary for patients with mild renal dysfunction (creatinine clearance 61–90 mL/min/1.73 m²). In patients with significant renal impairment (creatinine clearance <60 mL/min/1.73 m²), the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects).

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Cervastatin sodium demonstrated no effect upon non-stimulated cortisol levels and no effect on thyroid metabolism as assessed by TSH. Clinical studies with other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce plasma testosterone concentration. In rare cases, however, impotence may occur following their administration. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with cervastatin sodium who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs, e.g., ketoconazole, spironolactone, or cimetidine, that may decrease the levels of endogenous steroid hormones. (See DRUG INTERACTIONS, Cytochrome P-450 Inhibitors).

DRUG INTERACTIONS

Concomitant Therapy with Other Lipid Metabolism Regulators: Combined drug therapy should be approached with caution as information from controlled studies is limited.

Bile Acid Sequestrants: Co-administration of cervastatin sodium and cholestyramine resulted in a 22% decrease in cervastatin plasma concentration (AUC). Administration of cholestyramine 1 hour before the evening meal and cervastatin sodium 4 hours after the same evening meal resulted in a decrease in the cervastatin plasma concentration of less than 8%. Therefore, it would be expected that a dosing schedule of cervastatin sodium given at bedtime and cholestyramine administered before the evening meal would not result in a significant decrease in the clinical effect of cervastatin sodium.

Gemfibrozil, Fenofibrate and Niacin: Myopathy, including rhabdomyolysis, has occurred in patients receiving HMG-CoA reductase inhibitors with fibric acid derivatives and niacin (in lipid-lowering doses), particularly in subjects with pre-existing renal insufficiency (see WARNINGS, Muscle Effects).

Erythromycin: Co-administration of erythromycin 500 mg bid, a known inhibitor of cytochrome P-450 3A4, with cervastatin sodium 0.3 mg qd during 10 days in hypercholesterolemic patients resulted in a 50% increase in cervastatin AUC and in a 24% increase in C_{max} (see WARNINGS, Pharmacokinetic Interactions and Muscle Effects; PRECAUTIONS, P-450 Inhibitors).

Azole Antifungals: Co-administration with the antifungal agent itraconazole 200 mg qpm, another potent CYP3A4 inhibitor, and cervastatin 0.3 mg qpm during 10 days in hypercholesterolemic patients resulted in a 40% increase in cervastatin steady-state plasma concentrations (see WARNINGS, Pharmacokinetic Interactions and Muscle Effects; PRECAUTIONS, P-450 Inhibitors).

Calcium Channel Blockers: Co-administration of a single dose of 60 mg nifedipine extended release and cervastatin sodium 0.3 mg to hypercholesterolemic patients did not show any effect on either nifedipine or cervastatin plasma concentrations.

Coumarin Anticoagulants: Co-administration of warfarin and cervastatin sodium had no effect on the plasma concentration of either agent.

Digoxin: Co-administration of cervastatin sodium and digoxin resulted in a <10% increase in plasma digoxin levels. Patients taking digoxin should be monitored appropriately when cervastatin sodium therapy is initiated. Digoxin did not alter the pharmacokinetics of cervastatin.

Antacid (Magnesium-Aluminum Hydroxide): Co-administration of antacid with cervastatin resulted in an approximate 10% decrease in the cervastatin plasma concentration.

Cimetidine: Co-administration of cervastatin sodium (0.2 mg) with cimetidine (400 mg) resulted in an 11% decrease in the cervastatin plasma concentration.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies cervastatin sodium was used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, diuretics, estrogen replacement therapy, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence to date of clinically significant adverse interactions.

Cytochrome P-450 Inhibitors: Cervastatin is metabolized via a dual metabolic pathway utilizing at least two cytochrome P-450 isoenzymes, CYP2C8 and CYP3A4. Although not complete in some cases, a compensatory effect is observed when one pathway is inhibited. When co-administered with erythromycin, a known inhibitor of cytochrome P-450 isoform 3A4, cervastatin plasma concentrations increased by 50%. Drugs or common agents such as grapefruit juice that inhibit this enzyme may represent a potential for drug interactions when combined with cervastatin. Caution should thus be exercised with concomitant use of drugs such as immunosuppressants, antifungal agents (e.g., itraconazole, ketoconazole), macrolide antibiotics including erythromycin, antidepressants (e.g., nefazodone) or grapefruit juice (see WARNINGS, Muscle Effects and PRECAUTIONS, Endocrine Function).

with severe hypercholesterolemia; Higher drug dosages (0.3 or 0.4 mg/day) required for severe hypercholesterolemia are associated with increased plasma level of cerivastatin. Caution should be exercised in such patients who are also significantly renally impaired, or are concomitantly being administered digoxin, erythromycin or other cytochrome P 450 inhibitors (see WARNINGS, Muscle Effects; PRECAUTIONS; DRUG INTERACTIONS). Drug/Lab Interactions: HMG-CoA reductase inhibitors may elevate CPK and transaminase levels (see ADVERSE REACTIONS, Laboratory Tests). In the differential diagnosis of chest pain in a patient on therapy with BAYCOL, cardiac and non-cardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

BAYCOL® (cerivastatin sodium) is generally well tolerated. Adverse events have usually been mild and transient. In 2205 patients treated in placebo-controlled clinical studies investigating doses of 0.2 mg to 0.4 mg, 2.1% of patients were discontinued due to adverse reactions attributable to BAYCOL®, compared to 2.4% for placebo. Of these 2205 patients, 1298 were treated for ≥1 year. Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of BAYCOL® 0.2 to 0.4 mg/day and reported to be possibly, probably, or definitely drug-related are shown in the following table.

Associated Adverse Events Reported in ≥1% of Patients in Placebo-Controlled Clinical Trials of 0.2, 0.3 or 0.4 mg BAYCOL®		
	Placebo % (n = 861)	BAYCOL® % (n = 2205)
GASTROINTESTINAL		
Dyspepsia	2	1
Flatulence	1	1
Diarrhea	2	1
Constipation	2	1
Nausea	<1	1
NERVOUS SYSTEM		
Headache	1	1
Asthenia	1	1

Ophthalmological Observations: See PRECAUTIONS, Effect on Lens.

Laboratory Tests: Increases of serum transaminases and CPK have been noted in clinical trials (see WARNINGS).

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with cerivastatin therapy: myopathy, muscle cramps, rhabdomyolysis, arthralgias, myalgia, dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, vertigo, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression, psychic disturbances, pancreatitis, hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis (rare), fulminant hepatic necrosis (rare), hepatoma (rare), anorexia, vomiting, alopecia, pruritus, gynaecomastia, loss of libido, erectile dysfunction, progression of cataracts (lens opacities), ophthalmoplegia.

Hypersensitivity: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, dermatomyositis, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme including Stevens-Johnson syndrome.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The maximum single oral dose of cerivastatin sodium received by healthy volunteers and patients is 0.8 mg. No specific recommendations concerning the treatment of an overdosage can be made. Should an overdose occur, it should be treated symptomatically and supportive measures should be undertaken as required. The ability of cerivastatin and its metabolites to be dialyzed in humans is not known.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet (at least equivalent to the American Heart Association [AHA] Step 1 diet) before receiving BAYCOL® (cerivastatin sodium) and should continue on this diet during treatment with BAYCOL®. If appropriate, a program of weight control and physical exercise should be implemented.

The recommended starting dose is 0.2 mg once daily in the evening. The recommended dosing range is 0.2–0.4 mg as a single dose in the evening. BAYCOL® may be taken with or without food since there are no apparent differences in the lipid-lowering effects of BAYCOL® administered with the evening meal or at bedtime. Dosages should be individualized according to the recommended goal of therapy and the patient's response.

Since the maximal effect of a given dose of BAYCOL® is seen within 4 weeks, periodic lipid determinations should be performed at this time and the dosage adjusted to the patient's response to therapy and established treatment guidelines.

Consideration should be given to reducing the dosage of BAYCOL® if cholesterol levels fall below the targeted range, such as that recommended by the Second Report of the U.S. National Cholesterol Education Program (NCEP) and/or the Canadian Consensus Conference Guidelines.

Severe Hypercholesterolemia: In patients with severe hypercholesterolemia, higher dosages (0.3–0.4 mg/day) may be required (see WARNINGS, Muscle Effects; PRECAUTIONS; DRUG INTERACTIONS).

Concomitant Therapy: See PRECAUTIONS; DRUG INTERACTIONS.

Dosage in Patients with Renal Insufficiency: See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance: Cerivastatin sodium

Chemical Name: (+)-[3R,5S,(E)]-sodium-7-[4-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl]-3,5-dihydroxyhept-6-enoate

Molecular Formula: C₂₆H₃₃FN₂O₅Na

Molecular Weight: 481.5

Description: Cerivastatin sodium is a white to almost-white amorphous powder (lyophilisate). It is soluble in water, methanol and ethanol. The pK_{a1} is 5.8 and pK_{a2} is 4.4 determined using a 0.01g/L solution. The partition coefficient of cerivastatin was determined in octanol/phosphate buffer pH = 7 (log P = 3.0) and octanol/phosphate buffer pH = 5 (log P = 2.0) at room temperature. Cerivastatin remains solid up to 200°C. At higher temperatures, the active ingredient decomposes without melting.

Composition: BAYCOL® (cerivastatin sodium) tablets contain 0.2, 0.3 or 0.4 mg of cerivastatin sodium. Nonmedicinal ingredients: crospovidone, magnesium stearate, mannitol, povidone 25, sodium hydroxide, hydroxypropyl methylcellulose, polyethylene glycol 4000, titanium dioxide and ferric oxide.

Stability and Storage Recommendations: The tablets should be stored between 15° and 25°C. Dispense in tight containers.

AVAILABILITY OF DOSAGE FORMS

BAYCOL® (cerivastatin sodium) is supplied as 0.2 mg, 0.3 mg and 0.4 mg tablets. The different tablet strengths can be identified as follows.

Strength	Colour	Markings
0.2 mg	light yellow-brown	283 on one side, 200 MCG on the other
0.3 mg	yellow brown	284 on one side, 300 MCG on the other
0.4 mg	ocher	285 on one side, 400 MCG on the other

BAYCOL® is supplied in bottles of 100 tablets.

The tablets should be stored at room temperature (15° to 25°C).

Product monograph available on request.

REFERENCES:

1. Data on file. Pooled efficacy Analysis – Studies 149, 161, 162 and 182. 2. Data on file. Cerivastatin study no. 161 (IN PRESS). 3. Stein E. Cerivastatin in primary hyperlipidemia: a multicenter analysis of efficacy and safety. Am J Cardiol 1998;82:40J-46J. 4. Muck W. Rational assessment of the interactions profile of cerivastatin supports its low propensity for drug interactions. Drugs. 1998;56(Suppl. 1):15-23

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A Case for Osler

Catherine Chung, B.Sc. (OT3)
 Martin C. Chang, Ph.D. (OT3)
 Damon Scales, MD

Case Presentation

A 50 year old man who lives alone was found by his family lying in bed fully clothed. He was incontinent of urine, disoriented, and agitated. He was brought to the emergency department, where he was assessed to be acutely confused, tremulous, and febrile. The patient had admitted to drinking 6 beers the previous day. An interview with his family revealed that he had a history of heavy alcohol consumption and that he was a 1 pack-a-day smoker.

Discussion

What caused the confusion?

The history of alcohol abuse readily links the confusion to alcohol intoxication or withdrawal. Tremor with confusion is often seen in alcohol or drug withdrawal, and it is possible that the patient is suffering from alcohol withdrawal following his binge drinking the previous day. Although it is tempting to attribute the tremor to alcohol withdrawal, there may exist other explanations for this presentation, including other drug use, anxiety, stress, thyrotoxicosis, and asterixis from liver failure. Signs of alcohol withdrawal usually begin 6 to 24 hours after a decrease in the usual intake of alcohol. Symptoms range from mild withdrawal with insomnia and irritability to major withdrawal with autonomic hyperactivity (e.g. fever, tachycardia, diaphoresis), disorientation, and hallucinations.¹ A small percentage of patients experiencing alcohol withdrawal may develop generalized seizures. Delirium tremens, a rare but most severe form of alcohol withdrawal that usually develops 72 to 96 hours after cessation of drinking, is diagnosed when the course of withdrawal includes confusion, severe agitation, and visual, tactile, or auditory hallucinations.²

Other conditions related to excessive alcohol use that can lead to confusion need to be investigated such as mixed alcohol and drug overdose or withdrawal, alcohol-induced hypoglycemia, Wernicke's encephalopathy from thiamine deficiency, and hepatic encephalopathy (usually in the presence of underlying cirrhosis). Because falls are more likely in an alcoholic person, the patient should be examined for occult head trauma, which would raise the suspicion for the presence of intracranial hemorrhage or subdural hematoma. Other possible causes of confusion unrelated to alcohol abuse should be considered, including infections, hypoxia or hypercapnea, electrolyte disturbances (hyponatremia, hypernatremia or hypercalcemia), or endocrine disorders (Addison's disease, hypothyroidism). Structural abnormalities that can cause confusion include central nervous sys-

tem neoplasms and vascular disorders such as subarachnoid hemorrhage. The presence of fever may indicate sepsis, drug ingestion, anti-cholinergic poisoning, or intracranial hemorrhage. Indeed, an infectious process must always be considered whenever a patient presents with fever and a decreased level of consciousness. In particular, central nervous system infections such as meningitis or encephalitis should be suspected, but other infections such as pneumonia or urinary tract infection can also cause marked changes in mental status. An underlying psychiatric disorder manifesting as confusion, such as in acute mania and depression, cannot be dismissed and may coexist with the alcoholism.²

Case Presentation

Further examination revealed a depressed level of consciousness with eyes opening to voice but not to command, spontaneous movement of limbs, a supple neck, clear chest sounds and a soft abdomen. Blood pressure was 116/80, heart rate 123 bpm, respiratory rate 28/min, 92% O₂ saturation on room air and temperature 39.5°C. The toxicology screen was negative, including ethanol, ASA, and acetaminophen. The rest of the blood lab results are shown in Table 1. The patient was subsequently diagnosed empirically with delirium tremens and given thiamine, valium and normal saline.

Table 1
Blood Lab Results

Hemoglobin	114 g/L (135-175)
Chloride	90 mmol/L (98-106)
WBC	19.4 x 10 ³ cells/μl (4.5-11 x10 ³)
Bicarbonate	32 mmol/L (22-28)
PMN	85% (57-67%)
Calcium	1.98 mmol/L (2.10-2.55)
Platelet count	200 x 10 ³ cells/μl (250-450 x10 ³)
Phosphorus	0.68 mmol/L (0.87-1.45)
MCV	93 (80-100)
Magnesium	0.98 mmol/L (0.65-1.05)
PTT	31.5s (20-35)
AST	47 U/L(10-31)
INR	1.0 (0.87-1.11)
ALT	20 U/L (8-20)
Creatinine	73 μmol/ L (62-115)
ALP	226 U/L (53-128)
Sodium	131 mmol/L (136-146)
GGT	80 U/L (8-50)
Potassium	3.3. mmol/L (3.5-5.1)
Glucose	5.9 mmol/L (3.9-5.8)

Discussion

What is the significance of the results?

A depressed level of consciousness is a hallmark of an acute confusional state, and can help to differentiate it from acute psychosis. The negative toxicology screen and normal anion gap decrease the likelihood of a drug-related cause for the acute confusion. Although the leukocytosis could signify an infectious process, this finding alone is not specific. The normal glucose level helps to exclude hypoglycemia or hyperglycemia as the cause of his confusion. Chronic alcoholic patients often have poor nutrition, which may be reflected in the laboratory tests as decreased Hb, Ca^{2+} , PO_4^{3-} and Mg^{2+} . The elevated bicarbonate levels may reflect a metabolic alkalosis, which could be due to vomiting or to a contraction alkalosis. The elevated liver enzymes and AST:ALT ratio of 2:1 are consistent with alcoholic hepatitis. The normocytic anemia could represent either an anemia of chronic disease or a recent bleed, and requires further investigation.¹

What would be your approach to this patient?

Chronic alcohol consumers are often depleted in thiamine, and are thus given thiamine to prevent Wernicke's encephalopathy. Valium is given to counteract the effects of alcohol withdrawal and to prevent alcohol-related seizures. Although alcohol withdrawal leads to autonomic hyperactivity, the fever, tachypnea and tachycardia combined with the neutrophilia raises the suspicion of an infection. Malnutrition and underlying cirrhosis may also lead to an immunocompromised state. For instance, chronic alcoholics with cirrhosis are reported to have spontaneous development of bacteremia, peritonitis, a higher incidence of bacterial endocarditis, and an increased mortality rate in pneumococcal meningitis.¹

It has been observed that the likelihood of developing severe withdrawal symptoms increases with concomitant infections or medical problems. In fact delirium tremens is rare and seldom appears before the third post-abstinence day. Therefore, it is necessary to do blood cultures and Gram staining for the possibility of an infectious process. Chest x-ray should be performed, as pneumonia is the most common infection found in alcoholism. As previously mentioned, meningitis must be considered whenever a patient has fever and neurologic symptoms (e.g., confusion).² A lumbar puncture (LP) is required for sampling the CSF and empiric antibiotic therapy should be instituted promptly. However, a CT scan should be done prior to the LP if the patient is suspected of having increased intracranial pressure (depressed level of consciousness, focal neurologic deficits, papilledema, absent venous pulsations on fundoscopy), as failure to do so can lead to herniation of the brain. Since head trauma cannot be ruled out in this patient, it is important to perform a CT scan first.

Case Presentation

Subsequent assessment showed persistent confusion and a fluctuating level of consciousness. His blood pressure was 105/70, temperature 40.5°C, heart rate 120 bpm, respiratory rate 28/min. He had nuchal rigidity and a positive Kernig's sign (both signs of meningitis). Respiratory auscultation revealed decreased air entry in both lung bases with crackles at the right

base. There were normal first and second heart sounds with a 1/6 systolic flow murmur along the left sternal border. Further history revealed a two-day history of fever, chills and a cough productive of yellow sputum. Chest x-ray showed an infiltrate in the right lower lung field. The patient was started empirically on ceftriaxone and erythromycin for pneumonia. The CT scan of the head was unremarkable and results from the LP are shown in Table 2. Blood culture and Gram stain showed Gram-positive diplococci, but there was no growth from the CSF culture. Vancomycin was added to the treatment to ensure adequate coverage for a penicillin-resistant strain of Gram-positive diplococci.

Table 2
LP Results

CSF glucose	0.1 mmol/L (2.78)
Serum glucose	5.3 mmol/L
	(ratio 0.02; normal CSF: blood glucose ratio ≥ 0.6)
CSF protein	4.3 g/L (0.2-0.5)
WBC	4130 cells/ μL (0-6), Neutrophils 80% (none)

Discussion

How do you interpret the LP results?

The relative levels of glucose, protein and WBC in the CSF can help to distinguish between acute bacterial meningitis and viral meningitis. In bacterial meningitis, leukocyte numbers are usually greater than 1000/ μL (less increase in viral) of which neutrophils comprise greater than 50% (less than 10% in viral). Cerebrospinal protein content in bacterial meningitis is typically increased to greater than 1 g/L (usually only slightly elevated in viral meningitis), and glucose concentration is decreased to less than 2.2 mmol/L (normal CSF glucose in viral).⁴ Further evidence of bacterial meningitis may be obtained through the determination of the ratio of CSF glucose to serum glucose (typically decreased to less than 0.3 in bacterial meningitis). His LP results are certainly consistent with meningitis of bacterial etiology. The negative CSF culture is likely due to the use of antibiotic treatment before performing the lumbar puncture. Other explanations for a negative CSF culture with (usually mild) pleocytosis include non-bacterial causes such as viral meningoencephalitis, parameningeal infection, neoplastic disease, subarachnoid hemorrhage, trauma, and fungal or mycobacterial meningitis.

How did the patient get pneumonia and acute meningitis?

Although alcoholic patients may contract a variety of bacterial pneumonias, *Streptococcus pneumoniae* is the most common organism isolated. The increased incidence of pneumonia may be in part due to aspiration, facilitated by a depressed cough reflex, during periods of alcoholic stupor. There is a delay in the neutrophilic response during alcoholic intoxication that permits the spread of infection. Bacteremia occurs if the body is unable to localize the pulmonary infection by failure of local defense mechanisms in the lung. Metastatic infection secondary to bacteremia may occur in locations such as the meninges, joints, peritoneum or endocardium. *S. pneumoniae* typically cause meningitis once localized to the CNS but rarely cause encephalitis and it is the most common causative agent of meningitis in adults.⁴

Case Presentation

The following day, the patient was found to have a persisting fever of 38.7°C with confusion. His blood pressure was 110/70, heart rate 104 bpm, and respiratory rate 28/min. During the cardiovascular examination, the same 1/6 systolic flow murmur could be heard on the left sternal border. However, further careful examination by the resident revealed a new 2/6 early decrescendo diastolic murmur along the left sternal border, which was present during 1/3 of diastole. The patient's blood culture results confirmed *S. pneumoniae* sensitive to penicillin and ceftriaxone. His medications were subsequently switched to intravenous penicillin.

Discussion

What is the cause of the new heart murmur?

Early decrescendo diastolic murmurs are generally heard with aortic or pulmonic regurgitation, whereas mid-diastolic murmurs usually arise from the AV valves. Radiation of the murmur along the left sternal border is usually indicative of aortic regurgitation. The most common causes of acute aortic regurgitation are acute infective endocarditis, aortic dissection, and trauma. Given his current infection and bacteremia with *S. pneumoniae*, his new heart murmur is most likely due to infective endocarditis. The critical diagnostic finding in endocarditis is bacteremia, which was present in this patient. There has also been an association demonstrated between alcoholism and pneumococcal endocarditis.

Case Presentation

An urgent echocardiogram was performed which found a mildly dilated left ventricle with normal functioning and a normal right ventricle (Figure 1). There was slight thickening of the aortic valve with a mass lesion in the left ventricular outflow tract attached to the non-coronary cusp. The mitral valve exhibited increased echoes on the atrial side of the posterior leaflet.

Discussion

S. pneumoniae, which can attack normal valves, is more likely to occur on the aortic valve leading to rupture or perforation of the cusps. Concomitant infection of the mitral valve is often seen. With destruction of the aortic and mitral valves, the risk of heart failure is markedly increased. Complications of aortic valve endocarditis include the development of a perivalvular abscess and conduction defects resulting from invasion of the ventricular septum. Surgery to replace the infected valve(s) is indicated when positive blood cultures persist during therapy or when relapse occurs after appropriate therapy. Urgent surgery is required in patients developing intractable heart failure, myocardial or valve-ring abscesses, or when there are recurrent emboli.⁵

The clinical triad of pneumococcal pneumonia, meningitis and endocarditis in an alcoholic patient was first described by William Osler in 1882. Now rarely seen, it is commonly referred to as the "Austrian syndrome", named after Robert Austrian who wrote a review on the clinical triad.⁶

Epilogue

The patient was transferred to ICU for increasing respiratory distress requiring intubation for pulmonary toilet. A few days later, this culminated in acute pulmonary edema with pink frothy sputum, which was treated successfully with furosemide. It was decided that he required cardiac surgery. During the valve replacement surgery, it was found that his aortic valve leaflets were destroyed and there was a 15 x 15 mm vegetation on the aortic valve. An abscess was found extending into the wall of the left atrium and a vegetation was found on the P3 scallop of the mitral valve.

The patient was extubated successfully and soon afterwards, his level of consciousness improved. No residual neurologic deficits were noted. He was discharged two weeks later with a plan to complete a four-week course of penicillin.



Figure 1. transesophageal echocardiogram demonstrating vegetations on the aortic valve and mitral valve. Ao = aorta, LA = left atrium, LV = left ventricle, veg = vegetation

Clinical Pearls

- With any patient, it is important to do a proper and thorough physical examination both at the time of presentation and during follow-up assessments. The diagnosis of infective endocarditis could have been missed in this case had the resident not performed a scrupulous physical examination that picked up the new heart murmur.
- Even when a diagnosis may seem obvious at the time of presentation, it is important to keep a broad differential.

"Osler closed his lecture by reassuring the students he had seen several cases of delayed resolution in pneumonia.....But he also showed the diseased lung of a feeble old drunkard who had died in the hospital, and he reminded them of the lesson they had learned at the bedside of another patient the day before:..."

"... The proper diagnosis of the young man on Osler's ward who had been thrashing around, restrained by two attendants, and talking to an imaginary person was pneumonia, not delirium tremens." (*Summer Session Clinics. 1882,3,4.*)

From "William Osler, *A Life in Medicine*" by Michael Bliss, 1999.

Acknowledgements

The authors express their appreciation to Jim Graba for his assistance in selecting the images.

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Interstitial Laser Photocoagulation: A Clinical Alternative

Lee Chin, B.Sc.
Vanessa Choy, B.A.Sc.

Abstract

Interstitial laser photocoagulation (ILP) is an experimental cancer procedure whereby solid tumors are treated using laser energy by heating to high temperatures. As in all cancer treatments, ILP aims to target the tumor site while minimizing damage to healthy surrounding tissue. Significant research in this field has been progressing on two key fronts: 1) monitoring and control of thermal damage and 2) understanding and modeling the mechanisms by which thermal lesions occur.

This article offers a brief overview of ILP, concentrating primarily on the current research surrounding ILP. In addition, it discusses the role of thermal treatments in cancer therapy and offers some insight into the continuing developments required for the widespread implementation of ILP in medicine.

Introduction

In cancer therapy, a crucial balance must be achieved between treatment efficacy and quality of life. In particular, traditional methods such as radiation therapy, chemotherapy, and surgery, often induce injury to both undesired tumor tissue and healthy tissue (eg. whole body toxicity from chemotherapy, and prolonged discomfort from invasive surgery). Novel treatments that target tumor tissue while sparing surrounding healthy tissue are currently being developed at the Princess Margaret Hospital (PMH) in Toronto.

ILP is a therapy that is currently under development for the treatment of solid, unresectable tumors. During thermal therapy, tumours are heated to high temperatures (50 – 90°C) using a variety of heat sources including lasers, microwaves, and ultrasounds. In the case of ILP, laser energy is delivered using thin, flexible optical fibers (Figure 1). The laser must be powerful enough to induce a significant temperature rise in the tissue, and typically its power ranges from 2 – 10 W. To offer some perspective on the destructive capability of this treatment, most laser pointers emit light at powers of 5 – 6 mW, approximately 1000 times less than the power levels required for thermal damage. Tissue suffers a rise in temperature when the light energy from the laser is absorbed and subsequently excited by intrinsic tissue molecules called chromophores. Following photoexcitation, chromophores release the absorbed

energy in the form of heat. At elevated temperatures, the protein molecules in the tissue unfold and recombine in a process called thermal coagulation resulting in permanent irreversible damage. Following treatment, coagulated tissue is typically removed by sloughing and reabsorbed back into the body.

The key to thermal treatments is that energy sources are interstitially inserted into the tumor, thereby confining therapeutic temperatures specifically to the tumor volume. Under the guidance of ultrasound imaging, hollow needles are inserted percutaneously into the target site. The optical fibers are threaded throughout and the needles are then removed prior to heating the fibers. The minimally invasive nature of this treatment can greatly reduce the trauma caused by major incisions while targeting the tumor allows for aggressive treatment of the diseased tissue.

ILP appears promising as a minimally invasive technique for treating deep seated tumors or tumors located near vital structures.^{1,2,3}

Treatment Planning

One aspect of thermal therapy that is currently being researched is the development of models aimed at understanding the kinetic processes that govern the thermal damage of tissue. The hope is that models will offer physicians a thorough pre-clinical picture of the required input treatment parameters (eg. power, time of treatment, energy source) as well as the source positioning necessary for palliative/curative therapy.

Treatment planning models mathematically attempt to predict the 1) energy distribution from an applicator, 2) resulting increase in tissue temperature and 3) corresponding volume of cell death.⁴ Most models follow this simplified three step algorithm and are adjusted according to the desired energy source and target location. The resulting heat created and prospective tissue damage can be visualized as contours, and superimposed over images of the target organ (Figure 2).

Unfortunately, the accuracy of treatment planning models is complicated by non-linear changes in tissue properties that are a consequence of thermal damage to tissue. For example, vascular collapse from elevated temperatures significantly reduces blood perfusion, which in turn, affects local heating.⁵ Furthermore, research has demonstrated that tissue properties, which govern the scattering and absorption of energy, differ in native tissue compared to coagulated

Ontario Cancer Institute/Princess Margaret Hospital, Medical Physics Division,
University of Toronto, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9

(damaged) tissues.^{6,7,8} Hence, energy distribution varies dynamically during treatment. The effects of non-linear changes must, therefore, be accounted for in order to predict the final lesion created by the laser treatment.

Treatment planning provides a means of understanding the effects of various input parameters on treatment endpoints. However, induced thermal lesions are variable and somewhat unpredictable due to dynamic changes in blood perfusion and tissue optical properties during treatment. It is therefore important to include on-line monitoring and feedback control to compensate for these unknowns.

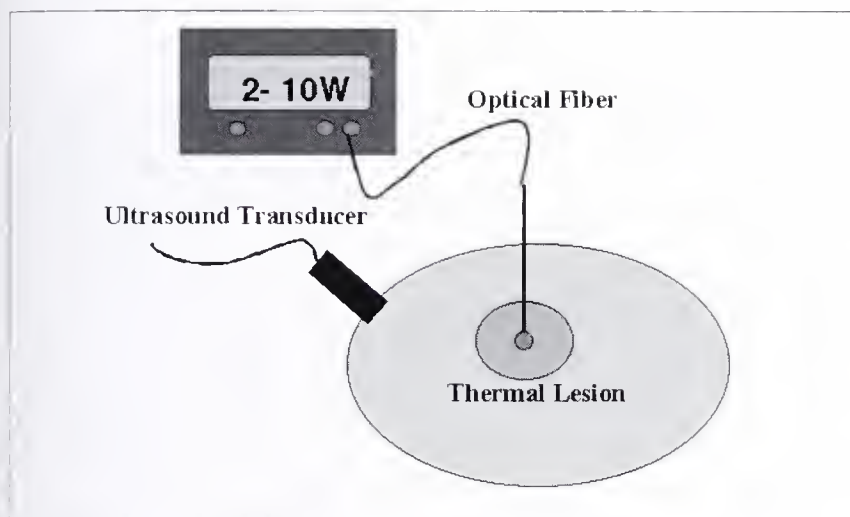


Figure 1. Schematic of typical interstitial laser photocoagulation treatment

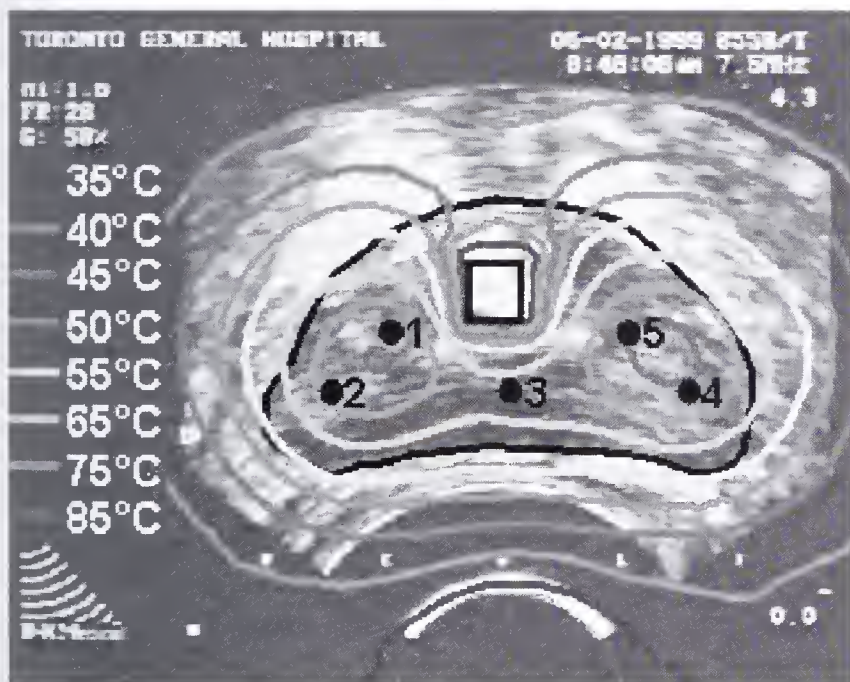


Figure 2. Damage contour calculated from a thermal therapy treatment planning program. Contour lines are overlaid over an ultrasound image of the targeted treatment area.

In-Line Monitoring

Feedback monitoring of key clinical markers allows for on-line optimization of input parameters to optimize treatment efficacy. In the case of ILP, the most relevant clinical markers are temperature and tissue damage. Temperature monitoring, or thermometry, is generally conducted using minimally invasive point probes, which is an economical alternative to expensive imaging systems. Though this method of monitoring does not offer instantaneous mapping of tissue damage, predictive models can be used in conjunction with

thermometry to provide real-time assessment of thermal lesion size.⁹ Sensors can be placed in strategic locations within the target tissue to monitor minimum treatment temperature and assess potential damage near critical structures. However, with the vast majority of the tissue temperature remaining unknown, complete assessment of treatment efficacy would remain difficult. As such, a number of investigators have examined the potential of non-invasive imaging techniques for monitoring ILP treatment including magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound.^{10,11} The key to image monitoring of ILP is to map the rapid thermal changes that occur in tissue structure during treatment. As examples, ultrasound monitoring of ILP relies on the differences in the acoustic impedance between native tissue and gas caused by microbubble formation, CT monitoring looks at changes in blood flow, and MRI imaging maps differences in the frequency shift (Larmor frequency) of protons due to tissue coagulation.

In addition to thermal damage, MRI techniques carry the added advantage of temperature sensitivity, allowing for three-dimensional (3-D) thermometry.¹² Recently, temperature maps have been combined with tissue damage models to predict the expected extent of damage.¹³ Due to its superior soft tissue contrast and potential predictive capabilities, MRI currently stands as the gold-standard by which ILP monitoring is assessed. Improvements in MRI and other imaging techniques will be vital for the continued advancement of ILP as a clinical tool.

Discussion and Ongoing Research

Thus far, this article has underscored the fundamental developments that have gradually allowed ILP to progress from research innovation to clinical tool. Given the relative novelty of ILP as a treatment procedure, one might naturally speculate of its place in the clinical setting and the necessary developments required for its widespread implementation.

Currently, ILP appears to be finding both a palliative and curative role in cancer therapy. Palliatively, ILP may be used in conjunction with other traditional therapies as a method for debulking large tumors or as a means of slowing rapidly developing cancer cells. Presently, ILP appears best suited for the possible curative treatment of smaller tumors, particularly in cases where resection is not an option. For example, 1) small, slow growing, colorectal or endocrine primaries of the liver, where surgery is inappropriate or 2) early cases of prostate cancer as an alternative to radical radiotherapy or surgery. However, increased clinical implementation of ILP will depend on its potential for safely treating large and irregularly shaped tumor sites. Improvements in defining the practical margins of thermal damage, planning the optimal treatment parameters and on-line feedback monitoring of thermal damage will also be required for increased ILP usage in cancer therapy.

Current research efforts are directed at improving imaging technology and increasing understanding of the biophysics behind thermal treatments. However, consideration must increasingly be given to practical issues including cost-effectiveness.

With increasing outbacks to healthcare, affordability must now be considered in the development of experimental treatments. Imaging devices, such as MRIs, are too expensive and impractical to be pur-

rely solely for ILP monitoring. In the past, temperature sensors have offered an economical alternative. However, temperature monitoring does not assess the rapid tissue response associated with high temperature thermal treatments. With the long characteristic thermal conduction times of tissues and large thermal gradients near the source fiber, temporal delays in detecting temperature change might not provide sufficiently fast feedback response to prevent tissue damage near the source. This is a practical concern as temperature sensors are placed strategically near vital structures, often at distances less than 1 cm from the source fiber.

At PMH, we are investigating the potential of minimally invasive light sensors as a potential alternative to current monitoring methods. This method takes advantage of the changes in the optical properties of tissue resulting from thermal denaturation and coagulation. Current research efforts are aimed at correlating the dynamic increases and decreases in light intensity during ILP with clinical events (eg. size, location of thermal damage). In the future, light monitoring will hopefully provide similar feedback to changes in tissue structure as imaging methods, but at a significantly reduced cost.

Although the concept and theory behind ILP has been present for over a decade, it is still a novel therapy foreign to the majority of the medical field. Currently, ILP technology is such that a typical treatment will require the presence of a radiologist and/or a technician.

Physicians, with full knowledge of the patient's history, and radiologists, with an understanding of treatment protocol, are necessary to properly control and monitor the progress of ILP. Thus far, expertise has largely been acquired through clinical experience and trial and error. Staff training can be both difficult and inefficient. However, if such expertise can be translated and implemented into an automated system, it can potentially reduce the dependency, or even eliminate the need for, on-site expertise.

A number of research efforts are currently focused on developing a control system for ILP application. The ultimate objective of control system research is to translate the human expertise into an easy to implement and reliable means of monitoring and controlling

treatment. Research into feedback-control will allow automated regulation of targeted endpoints based on temperature, light, or image maps. With such control systems in place, ILP may thereby progress from experimental innovation to clinical tool.

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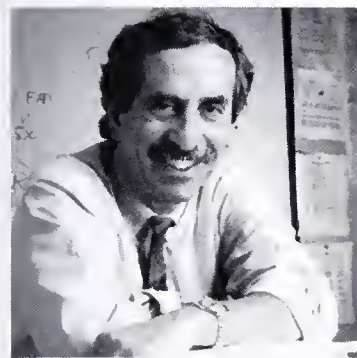
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Canadian Institutes of Health Research: A Genotype for Success

An Interview with Dr. Alan Bernstein

Jewel Samadder (OT3), B.Sc.H.



Dr. Alan Bernstein is the inaugural President of the Canadian Institutes of Health Research (CIHR). He is also a Professor of Molecular and Medical Genetics at the University of Toronto.

"Today the spirit of Banting and Best lives on in research facilities across Canada. CIHR will harness the energy, creativity and commitment of researchers in every health discipline ... translating this new scientific knowledge into better health for Canadians"

(CIHR advertisement in *Maclean's Magazine*).

Health research in Canada is at a defining point in its history, in a time of innovation and excitement, heralding a future bright with promise. A plethora of research discoveries in fields from molecular genetics to clinical drug trials are revolutionizing our understanding of the human genome and various diseases including cancer, diabetes, Alzheimer's disease and Cystic Fibrosis. These discoveries also reveal the interconnectedness of various research disciplines ranging from biomedical to clinical to socio-cultural and population health.

As of June 7, 2000, the Canadian Institutes of Health Research (CIHR) became the major federal agency responsible for funding health research in Canada, replacing the Medical Research Council (MRC). The objective of CIHR (as set out by Parliament) is to excel in the creation of new knowledge and translate this knowledge into improved health for Canadians, more effective health services and products, and a strengthened Canadian health care system. The mandate of the CIHR is wide ranging and inclusive, embracing all research that has the potential to impact on health – in contrast to the MRC's narrower focus on clinical and biomedical research. The first phase of CIHR's development involved the establishment of 13 virtual institutes which represent the continuum of research disciplines as well as the selection of their scientific directors (Table 1).¹ The University of Toronto – the leading biomedical research university in Canada – is well represented at CIHR. Four Institute directors (Genetics, Human Development and Child/Youth Services, Population and Public Health, Aboriginal Peoples Health), CIHR President Dr. Alan Bernstein and CIHR Governing Council member Dr. David Naylor (Dean of Medicine at U of T) all hold faculty appointments at U of T.

Many research disciplines that previously appeared to be polar opposites are beginning to realize their overlap. For example, diabetes can be investigated in terms of its genetics/immunology, its predis-

position in Aboriginals, and its impact on health service delivery and population health. Integration is occurring across disciplines as investigators discover that broader expertise enriches insight and accelerates discoveries. Some of the most exciting areas of new research connote this inter-disciplinary trend – bioinformatics, pharmacogenetics, bioethics, genetic epidemiology. The 13 institutes will enable researchers, voluntary health organizations, and government and private industries across Canada to work together to shape the national research agenda and translate findings into practice within Canada's health system.¹

Both the United States and Great Britain invest to a much larger extent in health research than Canada. The United States National Institutes of Health (equivalent to CIHR) spends over US\$14 billion annually on medical research.¹ In order to remain globally competitive and also to stem the "brain drain", Canada must invest in the science, minds, and leaders of the future. "We are looking into new ways to support the training of students and clinicians – research is all about people and attracting the best and brightest young people into a career in health research", says Dr. Bernstein.

In recent months, the Government of Canada has made a strong commitment to innovation and research excellence through funding for the Canada Foundation for Innovation, the Canadian Health Services Research Foundation (CHSRF), Millennium Scholarships, the Canada Research Chairs, Genome Canada and CIHR.² In a speech to the Toronto Board of Trade in September 2000, Finance Minister Paul Martin called on Canada to increase its investment in R&D and aim to rank Canada in the top five among OECD countries. The Minister continued, "Basic research creates ideas and pushes forward the frontiers of knowledge. Applied research transforms this knowledge into new products, services and technologies. We need to do more of both. And we need to do it better".

To ensure talented investigators/students are provided with the resources and training needed to address Canada's health needs, CIHR's budget will be \$402 million in 2000-2001, rising to \$533 million the following year. The Government has also promised another \$72 million in 2000-01 for electronic links – web sites, chat rooms – to connect scientists and their institutes. Alan Bernstein says the next step for Canada to remain globally competitive will be to double CIHR's budget to one billion dollars, or 1% of the country's total spending on health care.³

Today's students are tomorrow's scientists and leaders. Investment in research must parallel support for scientist training. The second

Table 1
CIHR Institutes and their Directors

Institute	Director	Directors' Home School
Cancer Research	Dr. Philip Branton	McGill University
Health Services and Policy Research	Dr. Morris Barer	University British Columbia
Aging	Dr. Rejean Hebert	University of Sherbrooke
Human Development and Child/Youth Services	Dr. John Challis	University of Toronto
Nutrition, Metabolism and Diabetes	Dr. Diane Finegood	Simon Fraser University
Musculoskeletal Health and Arthritis	Dr. Cyril B. Frank	University of Calgary
Population and Public Health	Dr. John Frank	University of Toronto
Genetics	Dr. Roderick McInnes	University of Toronto
Circulatory and Respiratory Health	Dr. Bruce McManus	University of British Columbia
Neurosciences, Mental Health and Addiction	Dr. Remi Quirion	McGill University
Infection and Immunity	Dr. Bhagirath Singh	University of Western Ontario
Aboriginal Peoples Health	Dr. Jeff Reading	University of Toronto
Gender and Health	Dr. Miriam Stewart	University of Alberta

phase of CIHR's program involves expanding financial support for research training from 1600 to 3000 scholarships, a 30% increase in salary awards for investigators, and increased investment in post-doctoral and clinician scientist awards.¹ "Training the next generation of researchers from across the entire health research spectrum is a high priority for us at CIHR", says Dr. Alan Bernstein. The new millennium heralds the conversion of insights gained from molecular genetics research (i.e. the Human Genome Project) into clinical application leading to better patient care. This will require an effective collaboration between scientists and clinicians, and will be a unique strength of clinician scientists. A committee has been assembled to analyze the future role of clinician scientists in Canada and the best options for their training. Alan Bernstein says he "supports graduate students, postdoctoral fellows and clinician scientist training, as well as career award support for junior faculty right up to the country's most distinguished health researchers".

Dr. Alan Bernstein is the inaugural president of the Canadian Institutes of Health Research. Bernstein is known internationally both as a researcher and scientific leader. He has made pioneering discoveries in areas of cancer and hematopoiesis, publishing over 180 refereed articles. Bernstein is a respected voice in Canadian research, having served advisory roles for the US National Cancer Institute, Alberta Heritage Foundation for Research, Canada's MRC, and the National Cancer Institute of Canada. Dr. Bernstein is a professor of Molecular and Medical Genetics at the University of Toronto and was formerly the Director of Research of the Samuel Lunenfeld Research Institute of Mount Sinai Hospital. Dr. Bernstein will continue to run his research laboratory in Toronto while administering to the nation's research agenda (CIHR) in Ottawa. "It's important that the head of the CIHR not only be a scientist, but that he be seen to be a scientist", says Bernstein. He believes his ongoing research will not only aid in his decision making at CIHR but will also send a message that the new organization is about doing cutting edge research, not publishing a paper.³ This is the same strategy adopted by Harold Varmus when he took over the US National Institutes of Health (NIH). Varmus, a Nobel Laureate in Medicine and currently the President of Memorial-Sloan Kettering Cancer Center in New York City, is excited by the prospects and direction of CIHR and its new president: "Someone like Alan who's perceived as a scientist, rather than a politician or

an administrator, brings a level of credibility to the job that's really important".³

The government's investment in CIHR will approach half a billion dollars in 2002. This will ensure Canada's place in the fast moving world of biomedical and health care research. This is a defining moment for health research in Canada. For the first time, Canada has a national organization that has the vision to lead our nation into the new millennium, a century of likely unprecedented biological and health research. "The next 10-15 years will be absolutely incredible for health research and the health care system. We are in the midst of a scientific revolution, a revolution that is being driven by a rapidly emerging understanding of the molecular basis of human biology and disease ... this revolution will ultimately transform our health care system", says Dr. Alan Bernstein.

"The benefits are clear. Improved health. A better quality of life. More responsive health services. A stronger health care system. An innovation based economy generating new ideas, products, services and jobs – attracting and retaining the best scientific minds".

(CIHR advertisement in *Macleans Magazine*).

For more information on CIHR you can visit their web site at www.cihr.ca.

Acknowledgements

I thank Dr. Alan Bernstein for providing the time for an interview for this article.

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Honest Truths About the Double Helix

Brenda Roy, M.Sc., Ph.D. (OT3)

A Passion for DNA: Genes, Genomes, and Society

James D. Watson

Cold Spring Harbor Laboratory Press
2000, 250 pp
\$38.95

The discovery of DNA's structure and role, in 1953, was arguably the most profound scientific event of the 20th century. Courtesy of Harvey, every child for centuries has learned that the heart pumps blood. Courtesy of Watson and Crick, every child now also learns that DNA is the blueprint of life.



Francis Crick and James Watson at Cold Spring Harbor Laboratory in 1990. Used with permission of Cold Spring Harbor Laboratory Archives.

The younger member of the DNA duo, James Watson, has achieved almost as much fame (and notoriety) for his writing as for his science. *The Double Helix*, first published in 1968, sold millions of copies and has been published in over 20 languages. So it was with much fanfare that Watson's latest book, *A Passion for DNA: Genes, Genomes, and Society*, was published. In this collection of essays old and new, Watson discusses the science and sociology of several issues – foremost are recombinant DNA, the war on cancer and the Human Genome Project.

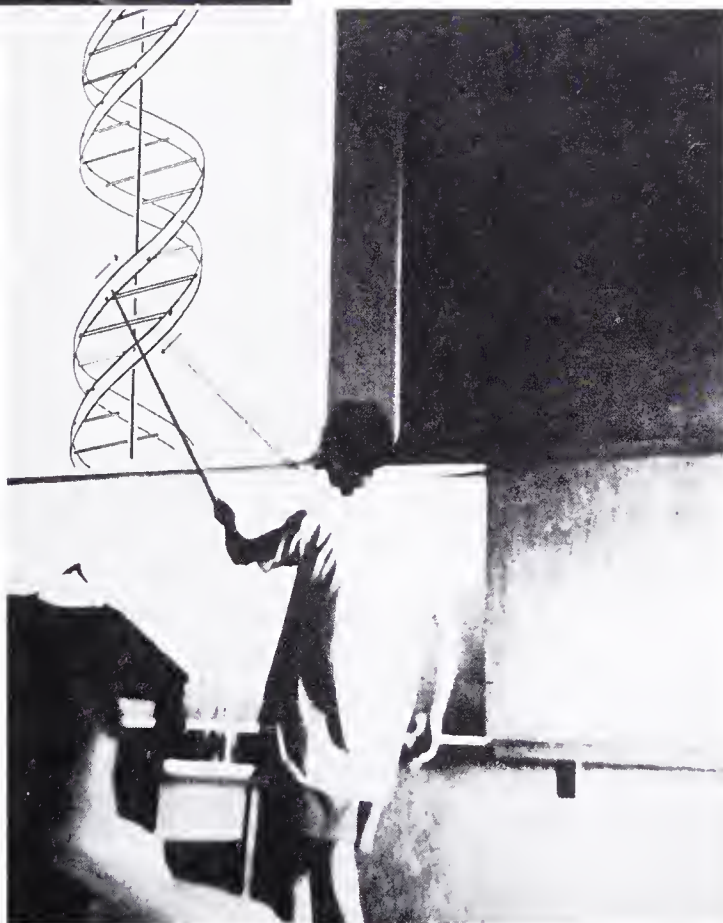
The book starts with an autobiographical discussion of the events in Watson's life that preceded his discovery of the double helix. He then

describes his scientific mentors, collaborators and rivals, as well as his philosophy on science. (Watson's advice for budding scientists: learn from the winners, take risks, have a fallback, have fun and stay connected.)

Watson then expands upon the history of two of the more controversial fields in molecular biology – recombinant DNA and the Human Genome Project. Pioneer recombinant DNA researchers felt that they should acknowledge what could potentially be generated by this new technology. Armed with that information, the public began to fear that DNA created in the laboratory would yield novel, highly pathogenic infectious agents. A moratorium on research and development was established in the mid 1970s until guidelines could be set up and the potential dangers of recombinant DNA investigated. Watson states, "it seemed more to the point to worry about what bad might come out of our labs rather than focus on the even more complex happenings that must occur naturally. That myopia, of which I also was guilty, will haunt us for a long time." His point regarding the early days of recombinant DNA and how it is "logically impossible to regulate conceptual risks" can be applied to any new scientific innovation: "[W]e mustn't overreact by assuming the worst possible outcome and settling into a siege response that prevents the possibility of progress ... we shall only harm ourselves by assuming that the newly developed recombinant DNA technology poses a credible threat to our civilization. The good that can come out of its use is immense."

Considering the recent announcement of the sequencing of the entire human genome by molecular biologists, the section in *A Passion for DNA* entitled 'Societal Implications of the Human Genome Project' is especially timely. Watson spends many pages addressing the historical issues that have led to the understandable emotional uneasiness the public feels towards genetics. Specifically, he discusses past American policies of sterilization and the eugenic atrocities committed in Nazi Germany, all conducted in the name of 'genetics'. These policies, however, were based on sloppy science and had more to do with the social milieu of the times than scientific truths. As Watson writes, "never again must genetics be seen as servants of political and social masters who need demonstrations of purported genetic inequality to justify their discriminatory social policies."

That genetics has a checkered past is undeniable. But should we let past errors stand in the way of current



James Watson gives a talk on the double helix in June 1953 at CSHL. Used with permission of Cold Spring Harbor Laboratory Archives.

research? Watson clearly does not want to repeat the mistakes made with recombinant DNA in the 1970s: “[I]nstead of solely focusing our ethical concerns on potential misuses of this new knowledge, we must also face up to the moral consequences of not acquiring and using this new genetic knowledge. Not moving ahead to prevent new cases of genetic diseases or to search for cures, when we have the means to do so, also has strong ethical implications.”

The public, of course, fears genetics not only because of past atrocities but also because it is a complex subject. So should the largely ill-informed public decide how society uses the fruits of molecular biology, or should these decisions be left to experts? Watson proposes education as a solution. A wider understanding of science could alleviate much confusion, and if we as a society are to make decisions that affect our descendants’ genetic makeup, we owe it to ourselves to become genetically literate.

Watson’s characteristically forceful views and lucid writing make for clear arguments – *A Passion for DNA* is strongest when Watson is expounding on the ramifications of scientific progress. However, in his noble attempt to give credit where credit is due when discussing scientific discoveries, parts of his book are heavy and dull. It is difficult to keep track of which names and dates go with which discovery and the reader may lose sight of Watson’s intended message.

Watson is flamboyant and outspoken, and readers may find themselves challenging his arguments. But in truth, Watson is merely a provocateur – whether you agree or disagree with his views is not of paramount importance. What is important is that this book brings to our attention the complex social issues associated with molecular biology. This book is highly recommended for those who wish to understand the ethical basis for the use of molecular biology in medicine. Today’s medical students may one day have the unprecedented ability to control a child’s genetic destiny – we owe it to society to consider the issue sooner rather than later.

Evolutionary Psychology for Dummies

Jennifer Gold

**Mean Genes.
From Sex to Money to Food:
Taming Our Primal Instincts**

Terry Burnham and Jay Phelan

Perseus Publishing
2000, 263 pp
\$36.50

On the very first page of *Mean Genes*, authors Terry Burnham and Jay Phelan describe the human brain as having a “mind of its own”, and indeed their book is marketed as a self-described “owner’s manual” for the brain. Essentially, *Mean Genes* is sociobiology for the

Everyman; indeed, a better title might have been *Evolutionary Psychology for Dummies*. The book runs, predictably, through genetic reductionism’s mainstay – namely food, finances, family, foes, and sex.

Unfortunately, *Mean Genes* offers little in the way of concrete human evidence to support its many examples. The authors rely mainly on animal studies, anecdotal reports and their own experiences. In the chapter entitled ‘Romance and Reproduction’, for instance, we are introduced to Jean, a friend of the authors. At a recent party, Jean, a woman of western European background, found herself “powerfully attracted” to Ali, a man of Middle Eastern heritage. Although Jean loved her current boyfriend, she immediately began an affair with Ali and ended her previous relationship. The authors cite this story as evidence that humans are most attracted to those who have different immune system markers from their own. No reason is given as to why we should accept this explanation rather than, say, that Jean was in reality dissatisfied with her boyfriend and looking for a way out, or that Ali was a master of seduction. Instead, Jean and Ali are depicted as prisoners of their biology, predestined to leave former suitors in an attempt to satisfy picky genes.

Mean Genes is also largely ineffective as the owner’s manual it purports to be. The introduction concludes by promising that the book will help readers to live more satisfying lives; lives with “integrity”. This help comes in the form of vague, ill-defined “advice” provided at the end of each chapter. In the chapter on food, for example, the authors teach us ways to avoid overeating and excess weight gain. These include “destroying” half a bag of chips before sitting down to eat them, and smearing mayonnaise on airline brownies to render them inedible. While these may indeed be effective deterrents, it is unlikely that either will be a long-term solution to obesity. One is also left wondering what integrity there is in smearing mayonnaise on a brownie.

To be just, the book is written somewhat tongue-in-cheek, and is moreover meant to be funny and readable. It is not an academic text, but it does not pretend to be one either, so perhaps it is unfair to expect much rigour. To their credit, the authors are enthusiastic about their work and it is obvious they believe what they write. Phelan, a biology professor at UCLA whose research is in evolutionary genetics, is a qualified source, though we are left to wonder what expertise Burnham, a business professor, lent to the project.

Writing for the general public, however, comes with an important duty of its own. Most people will never read the peer-reviewed articles of *Science* and *Nature*, and it is thus imperative that the information they obtain from popular non-fiction is accurate. Medical students especially must ensure that their han-

dle on genetics is both correct and balanced. Many diseases are currently being 'exposed' as genetic. It is, however, important to remember that many ailments have a strong environmental component – heart disease and diabetes to name just two. On the flip side, it is also crucial that illnesses such as depression and schizophrenia not be viewed as primarily environmental. For a better analysis of the arguments both for and against genetic determinism, I would steer readers in the direction of classic texts like Richard Dawkins' *The Selfish Gene* or Stephen Jay Gould's *The Mismeasure of Man*.

While some of the hypotheses put forth by *Mean Genes* may indeed prove to be correct, there is currently insufficient human data to definitively back these theories. It seems to me that the authors have a certain social responsibility in writing such a book. Until there exists conclusive evidence for some of the more outlandish claims of behavioral genetics, perhaps it would be best *not* to suggest people have little control over their behavior. Cheating spouses, murderous siblings, rapists – do we really want to advocate an unproven theory, which absolves scoundrels by giving them a genetic 'out'? Philosophy, theology, and a host of other disciplines generally pinpoint the difference between humans and other animals as conscience. We *choose* courses of action. Perhaps, one day, evolutionary biology will demonstrate that conscience is genetically determined, operating merely as a Darwinian tool. Until then, however, I will continue to firmly believe that I am in control of my destiny. After all, I never eat the airline brownie.

For the Voyeur within Us

Hemant Shah, B.ArtsSc. (OT3)

The Two-Headed Boy and Other Medical Marvels

Jan Bondeson

Cornell University Press
2000, 320 pp
\$46.50

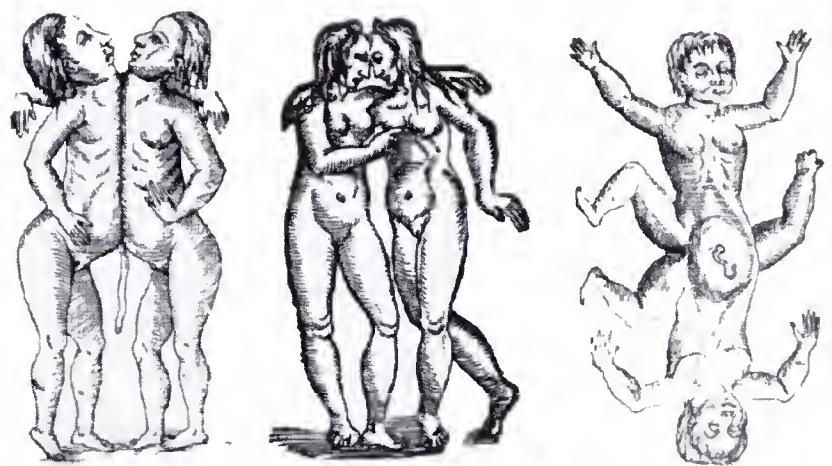
Any medical professor worth his salary knows that by projecting an outsized image of a 'freak' in front of a class of medical students, he is guaranteed to grab their attention. Conjoined twins will do, but a harpsichord-playing woman whose face is covered with hair is better. It is the pervasive human obsession with congenital anomalies like these that forms the basis of Jan Bondeson's *The Two-Headed Boy and Other Medical Marvels*.

Bondeson writes about these individuals from the perspective of "human interest," and his goal is to "approach them as human beings, born with sometimes appalling congenital deformities, and ... chronicle their lives and vicissitudes as closely as possible."

Bondeson's book is a historical study from primary sources. Therefore, like similar works on teratology such as *The Girl Who Gave Birth to Rabbits*, it is strongly rooted in the literature of the

patients' time. But unlike many similar works, Bondeson combines this cultural perspective with scientific rigour developed from his training as a physician. For example, the detailed description of Nicolas Ferry, the king of Poland's Court Dwarf in the mid-18th century, is preceded by a vivid analysis of the condition that led to his short stature and early demise. Bondeson guides us through potential diagnoses made by medical experts interested in Ferry; these include congenital syphilis in 1890, ateliosis in 1911, Seckel syndrome in the 1960s, and a "progeroid variant of osteodysplastic primordial dwarfism with more or less pronounced intrauterine growth retardation", the diagnosis now in vogue. This sort of clinical reasoning makes *The Two-Headed Boy* especially interesting for the medical professional.

This book also provides glimpses of insight for the student of social and cultural history. Many of the individuals profiled in the text are abused, exploited, displayed in travelling shows, and callously discarded when their novelty is spent. Yet, Bondeson writes with a tender empathy and in doing so, makes a strong statement about our own society. While we often marginalize those different from us, we should recall that these opinions are not unprejudiced. Bondeson reminds us of what Michel de Montaigne wrote in *Of Cannibals*: "[E]ach man calls barbarism whatever is not his own practice; for indeed it seems we have no other test of truth and reason than the example and pattern of the opinions and customs of the country we live in." Perhaps, as Bondeson has done, we will look upon our current practices in the future and expose them for their inherent discrimination.



Types of conjoined twins depicted by French renaissance surgeon Ambroise Pare. From *On Monsters and Marvels* (orig, 1573), University of Chicago Press, Chicago, 1982.

Overall, *The Two-Headed Boy and Other Medical Marvels* is a worthwhile read for the lay sociologist. From a social point of view, Bondeson provides colourful but objective descriptions of the circumstances and tales surrounding many remarkable patients. Scientifically, he evaluates legends and debunks apocryphal myths. The Two-Headed Boy not only brings us one step closer to understanding why the diagnosis is important, but it also illustrates that diagnosis alone does not define a 'medical marvel'.

And How Does that Make You Feel?

Stephanie R. Wiesenthal, B.Sc., M.Sc. (OT2)

The Psychiatric Interview: A Practical Guide

Daniel J. Carlat

Lippincott Williams and Wilkins
1999, 253 pp
\$39.95

The goal of the psychiatric interview is fourfold: first, to develop a therapeutic alliance with the patient; second, to better understand the patient; third, to generate potential diagnoses; and fourth, to formulate a treatment plan. Knowing the goals, however, is only the first step to performing

an effective diagnostic interview – also necessary are experience, training, and a few helpful hints.

The Psychiatric Interview: A Practical Guide by Daniel J. Carlat, is a straightforward, informative and humorous guide to conducting a comprehensive diagnostic psychiatric interview. Carlat, chief of psychiatry at a Massachusetts hospital, has an extensive background in psychiatry education. In addition to teaching primary care residents about psychiatric interviewing, he has also recently written *The Psychiatric Review of Symptoms: A Screening Tool for Family Physicians*. His latest book was born on a frustrating night during his psychiatric residency, where “as the night stretched on ... [his] interview got briefer ... until at 5 am [his] entire interview consisted of ‘are you suicidal?’” From this experience, Carlat recognized the need to develop a more rapid but thorough system for conducting a diagnostic assessment. His objective was to facilitate the proficiency and recall of the interviewer while reducing the frustrations inherent in conducting such an intensive interview.

The Psychiatric Interview is organized into four main sections. Section I deals with general principles of effective interviewing, including helpful hints on how to approach delicate topics like drug abuse or domestic violence. In addition, strategies to deal with challenging situations, such as the adolescent, hostile, seductive or tearful patient are included. When a patient cries, for example, a typical response might be to hand the patient a tissue while feeling somewhat ineffectual. Carlat suggests that an effective verbal response to a suddenly tearful patient might be: “What’s on your mind now as you’re crying?” This and other valuable responses are included in Section I. Section II includes valuable hints, sample questions and mnemonics to assist with the psychiatric history itself, which includes the history of present illness, the past psychiatric history, medical illnesses, family psychiatric history and the social and developmental history. For example, “When

was the last time you remember feeling perfectly well?” might be one way of beginning the history of present illness eventually followed by, “Now let’s talk about the current episode. When did it start?” Section III includes DSM-IV criteria, and mnemonics for remembering the different diagnostic categories and their criteria. Also included are screening questions for each diagnostic category, as well as the mini-mental status examination. The mnemonics are especially useful, as they assist with recall of an otherwise overwhelming mass of information. Finally, Section IV outlines how to construct a treatment plan and present the interview in written format. Carlat has also provided a practical appendix that includes pocket cards, patient education handouts, and both a short and long form of the psychiatric interview all summarized in a few short pages.

The Psychiatric Interview is well written and straightforward. Interspersed throughout each chapter are motivating and inspiring quotations that provide a creative setting for the book. A rarity for texts nowadays, *The Psychiatric Interview* is also inexpensive. As well, it is portable – useful for ward or call. Most importantly, the strategies offered by Carlat are not limited to psychiatric settings. The techniques for dealing with challenging clinical situations, such as the hostile patient, can be used in all medical settings. *The Psychiatric Interview* does not disguise itself as a replacement for psychiatric textbooks; instead, it successfully steers the novice interviewer to the fundamentals of psychiatric interviewing. The patient education handouts and psychiatric interview ‘cheat sheets’ provided in the appendix are especially valuable and can be used as a checklist or quick reference.

Some readers may find it irritating that *The Psychiatric Interview* reads more like a novel than a textbook, as this can significantly lengthen reading time. Others, however, may feel that the writing style is part of what makes the book interesting and a joy to read. Overall, *The Psychiatric Interview* succeeds as a brief, easy to read, and comprehensive guide to conducting a successful psychiatric diagnostic interview.

Neurological Bible Gets an Update

Paul S. Giacomini, B.Sc. (OT1)

Neurology in Clinical Practice, 3rd edition

Walter G. Bradley,
Robert B. Daroff,
Gerald M. Fenichel,
C. David Marsden

Butterworth-Heinemann
1999, 2720 pp
\$684.50

With recent advances in clinical neurology and neuroscience alike, as evidenced by the awarding of last year's Nobel Prize in medicine to three neuroscientists, an update of the acclaimed second edition of *Neurology in Clinical Practice*, published in 1996, was somewhat overdue. In its third incarnation, the authors have substantially revised and updated their text-

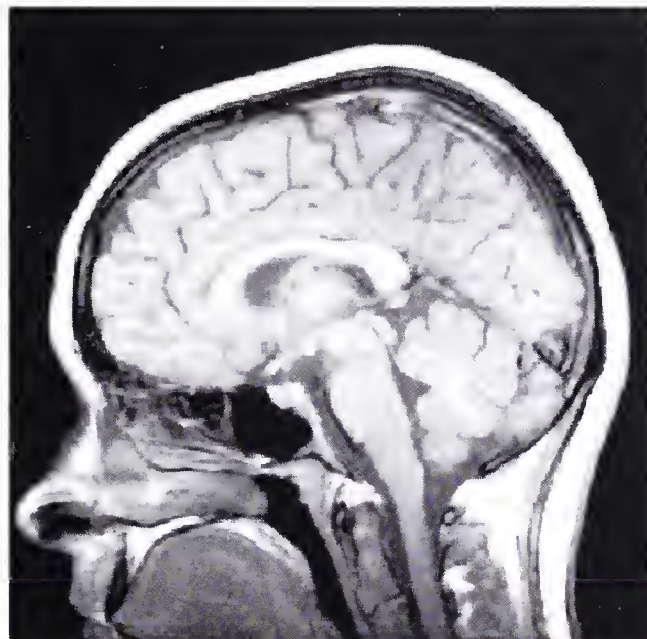
book to incorporate the latest advances from both the clinical and scientific fronts. The result is an extensive, yet elegant and comprehensive compendium of the principles and fundamentals of clinical neurology.

The book itself is divided into two beautifully bound volumes. The first volume covers the principles of diagnosis and management; the second examines the neurological disorders. Each chapter is covered in excellent depth and breadth and is penned by a world-renowned expert in a particular neurological subspecialty. Three University of Toronto professors are among the list of authors.

The first half of Volume One offers a brief yet complete synopsis of common neurological phenomena. The topics covered include loss of consciousness, intellectual and memory impairment, visual loss, vertigo, apraxias, muscle pain and cramps and many others. The beauty of these chapters is that they offer an approach to common presentations of neurological conditions, and discuss in detail the different features that enable one to diagnose a neurological disease. Several chapters also include a colourful historical anecdote that adds a new dimension of interest. The second half of Volume One examines neurological investigations and related clinical neurosciences. These nineteen chapters are comprehensive, but not excessively detailed. They cover topics such as neurophysiology, neuroimaging, neurology of the special senses and even neuropharmacology and therapeutics. Most of these chapters are further subdivided into key topics and include concise diagrams and tables to complement the text. This feature is of particular benefit in the chapters describing the neurology of the special senses where the illustrations of the neural pathways help considerably in clarifying the concepts.

Volume Two focuses on nervous system disorders. The first five chapters address a large scope of problems including neurologic complications of systemic disease, trauma, vascular disease, tumours and infections. Despite the large spectrum of disease encompassed under these headings, each chapter nevertheless succeeds in its goal of delivering a concise and complete synopsis of all the pertinent disorders. The remaining chapters in Volume Two focus on specific disorders such as encephalopathies, dementias, demyelinating diseases, movement disorders, disorders of the peripheral nerves, etc. These chapters are very well organized and provide the reader with a thorough description of the pathophysiology and treatment of each specific disease or class of disorders. Volume Two concludes with three chapters addressing neurology in the newborn, pregnant and geriatric patient.

Despite its enormous number of contributors, *Neurology in Clinical Practice* manages to maintain a consistent style of writing that makes the chapters enjoyable to read. Moreover, the book manages to avoid a common pitfall that entraps many of the 'bibles' of medicine; the authors cover a vast amount of material, but they do so without appearing overly laconic and they succeed in addressing their subjects with appropriate detail. Furthermore, all chapters are copiously referenced from recent articles culled from a variety of neuroscience journals. The fantastic illustrations and colour photographs also lend to the appeal of this great text. The vast majority of photographs and illustrations are in black and white yet they still achieve their purpose of reinforcing concepts and topics discussed in the text. Although limited in number, the colour photographs are beautifully printed on high quality glossy paper that sacrifices neither detail nor resolution.



Used with permission from P.A. Stewart, *Functional Neuroanatomy*, 2001, B.C. Decker, Inc. Philadelphia.

Overall, *Neurology in Clinical Practice* is an excellent textbook and a must-have for all neurology residents. Although the text is geared toward the resident or practising physician, it can still be of benefit to the undergraduate medical student with an interest in neurology. The one drawback of this otherwise superb text is its exorbitant cost. At close to \$700, it is far beyond the economic means of most medical students and junior residents. Nevertheless, it may be worth the investment, as this is truly the only book the aspiring neurologist will ever need.

A New Edition of a Medicine Standard

David Star, BSc, MSc (OT1)

Cecil Textbook of Medicine, 21st edition

Russell L. Cecil, J. Claude
Bennett, Lee Goldman

W. B. Saunders
2000, 2308 pp
\$201

Internal medicine is a general specialty – an oxymoron, but also a truism. Trainees, therefore, need a vast amount of basic medical knowledge in order to help them diagnose and treat the myriad of disease states that affect the human body. This makes internal medicine a particularly demanding field. To combat this stress, there are a variety of resource

books available to students. These include pocket reference books such as the *Washington Manual*, review books such as the *National Medical Series (NMS)*, and textbooks such as *Harrison's Principles of Internal Medicine* and the *Cecil Textbook of Medicine*. *Cecil's*, as it is known, is available both as a hardcover textbook, and a softcover summary version called *Cecil Essentials of Medicine*. Many medical students purchase *Essentials*; this review, however, deals with the more detailed textbook version of *Cecil's*, which is meant to compete with *Harrison's*.

Perhaps *Cecil's* biggest strength is its uniformity. Even though there are two editors, six consulting editors and 443 contributors, there is a certain consistency present from chapter to chapter, as well as within the different sections of a chapter (which are usually written by different contributors), that makes reading this book quite easy.

Another strength of this book is its organization. The book is divided into 28 chapters, with 18 colour plates. The chapters cover the basic specialties such as cardiology, respiratory, neurology, nephrology, etc. Each chapter is then subdivided into a variety of subchapters. Most of the topics throughout this textbook are covered with sufficient detail that rarely does one have to go to another source for more information. As a medical student this is very important, since medical trainees rarely have the time or the energy to read a variety of sources. Nevertheless, *Cecil's* manages to also cover aspects related to internal medicine that other textbooks generally do not. Examples of this are a chapter on critical care medicine, a chapter on preventative health care, a chapter on the principles of evaluation and management, and a chapter on the principles of human genetics.

Another unique feature of this textbook is the way that most chapters begin, with 'an approach to a patient'. Many books do not offer this feature, but it is extremely helpful for medical students. Another helpful feature is the medical imaging included in certain sections. Unfortunately, this idea was not well implemented, since very few images are shown in these sections. The colour plates cover topics such as gastrointestinal diseases, renal and nutritional diseases, infectious diseases and HIV associated disorders. Although the photographic quality is high, it would have been nice to see more pictures in each section. The tables and figures are very well done, and are usually quite readable.

The *Cecil Textbook of Medicine* is definitely an excellent book to own. It is a pity that it is so underused by medical trainees. At 2308 pages, it is not a book that one could read from cover to cover. Nonetheless, it is a very good resource for trainees and physicians alike.

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Brief Prescribing Information

NORVASC*
(amlodipine besylate)
Tablets 2.5, 5 and 10 mg
Antihypertensive-Antianginal Agent

ACTION AND CLINICAL PHARMACOLOGY

NORVASC (amlodipine besylate) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). Amlodipine is a member of the dihydropyridine class of calcium antagonists.

INDICATIONS AND CLINICAL USE

Hypertension

NORVASC (amlodipine besylate) is indicated in the treatment of mild-to-moderate essential hypertension. **NORVASC** should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. **NORVASC** can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of **NORVASC** with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.

Chronic Stable Angina

NORVASC is indicated for the management of chronic stable angina (effort-associated anginal) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. **NORVASC** may be tried in combination with beta-blockers in chronic stable angina, in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

CONTRAINDICATIONS

NORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines and in patients with severe hypotension (less than 90 mmHg systolic).

WARNINGS

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Outflow Obstruction (Aortic Stenosis)

NORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis).

Use in Patients with Impaired Hepatic Function

There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild-to-moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged. **NORVASC** should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSE AND ADMINISTRATION**).

Beta-blocker Withdrawal

NORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

PRECAUTIONS

Use in Patients with Congestive Heart Failure

Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that **NORVASC** had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.

Hypotension

NORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.

Peripheral Edema

Mild-to-moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Use in Pregnancy

Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with **NORVASC** in pregnant women. **NORVASC** should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, **NORVASC** should not be given to nursing mothers.

Use in Children

The use of **NORVASC** is not recommended in children since safety and efficacy have not been established in that population.

Use in Elderly

In elderly patients (>65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. **NORVASC** should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSE AND ADMINISTRATION**).

Interaction with Grapefruit Juice

Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice.

Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Co-administration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels. Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin. Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline. Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.

Cimetidine, Warfarin, Cyclosporin, Digoxin: Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated:

- **cimetidine** did not alter the pharmacokinetics of amlodipine.
- amlodipine did not change **warfarin**-induced prothrombin response time.
- amlodipine does not significantly alter the pharmacokinetics of **cyclosporin**.
- amlodipine did not change serum **digoxin** levels or **digoxin** renal clearance.

Acids

Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.

Beta-blockers: When beta-adrenergic receptor blocking drugs are administered concomitantly with **NORVASC**, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.

Sildenafil: A single 100 mg dose of sildenafil (VIAGRA) in subjects with essential hypertension had no effect on AUC, or C_{max} of amlodipine. When sildenafil (100 mg) was co-administered with amlodipine, 5 or 10 mg in hypertensive patients, the mean additional reduction of supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic.

Special Studies: Effect of **NORVASC** on other agents.

Atorvastatin: In healthy volunteers, co-administration of multiple 10 mg doses of **NORVASC** with 80 mg of atorvastatin resulted in no significant change in the AUC, C_{max} or T_{max} of atorvastatin

ADVERSE REACTIONS

NORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild-to-moderate severity

Hypertension

In the 805 hypertensive patients treated with **NORVASC** in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%). The following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials program (n=805):

Cardiovascular: edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%) **Skin and Appendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).

Angina

In the controlled clinical trials in 909 angina patients treated with **NORVASC**, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%). The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909):

Cardiovascular: edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%) **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** vision abnormal (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).

NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina. The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoesthesia, peripheral neuropathy, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** allergic reaction, asthenia, back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus, rash erythematous, rash maculopapular, erythema multiforme. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** hyperglycemia, thirst. **Hemopoietic:** leucopenia, purpura, thrombocytopenia

†These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, Stevens-Johnson syndrome, alopecia, twitching, ataxia, hypertonnia, migraine, apathy, amnesia, gastritis, pancreatitis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia. Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

SYMPTOMS AND TREATMENT OF OVERDOSSAGE

Symptoms

Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of **NORVASC** (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month-old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.

Treatment

Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As **NORVASC** is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

DOSE AND ADMINISTRATION

Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of **NORVASC** (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.

Use in the Elderly or in Patients with Impaired Renal Function

The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).

Use in Patients with Impaired Hepatic Function

Dosage requirements have not been established in patients with impaired hepatic function. When **NORVASC** is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

DOSE FORMS

Availability

NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

STORAGE

Store at 15-30°C. Protect from light.

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1. **NORVASC*** Product Monograph, Pfizer Canada Inc., April 2000.
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1. **NORVASC*** Product Monograph, Pfizer Canada Inc., April 2000.
2. Hernandez-Hernandez R *et al*. The effects of missing a dose of enalapril versus amlodipine on ambulatory blood pressure. Blood Pressure Monitoring 1996;1:121-6.
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1. Reinders FX, Chalin C, and Meier HMR. (1993). Alzheimer's disease: Understanding the patient and caregiver. *UTMJ*. 70: 16-20.
2. Kocsis JH, Davis JM, Katz MM, *et al.* (1985). Depressive behavioral and hyperactive adrenocortical function. *Am J Psychiatry*. 142: 1291-1298.

* Abbreviated journal titles should be used.

Articles **with more than 4 authors should include the first three authors followed by *et al.*

Article in a book or comparable publication

3. Smith MHD and Teele DW. (1995). Tuberculosis. *In: Infectious diseases of the fetus and newborn infant, 4th ed.* Remington JS and Klein JO (eds). WB Saunders: Philadelphia, pp. 1074-1086.
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Books, theses, or comparable publication

5. Pressaco J and Yu H. (1996). *Pharmacological Treatment of Diseases*. Urban and Schwarzenberg Medical Books Inc: Toronto.

NEW: Web documents

6. Jacobson, J. W., Mulick, J. A., & Schwartz, A. A. (1995). A history of facilitated communication: Science, pseudoscience, and antisense: Science working group on facilitated communication. *American Psychologist*, 50, 750-765. Retrieved January 25, 1996, from the World Wide Web: <http://www.apa.org/journals/jacobson.html>

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NORVASC*
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- effectively controls BP at target levels for a full 24 hours and beyond^{1,2†}
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‡ NORVASC* (n=114), 83% of NORVASC* patients remained on therapy after 48 months.

NORVASC* is indicated in the treatment of mild-to-moderate essential hypertension when diuretics or beta-blockers are unsuitable.

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